Management of non-cystic fibrosis bronchiectasis

Abstract

Bronchiectasis is a common respiratory condition, characterised by abnormal bronchial dilatation, that often leads to recurrent airway infection and inflammation. It is an increasingly recognised respiratory condition, both as a primary lung disease but also co-existing with other respiratory diseases, such as chronic obstructive pulmonary disease and asthma. Diagnosis can have important treatment implications. There are shared systematic approaches to treatment, such as sputum clearance techniques, prompt treatment of exacerbations and, in certain circumstances, regular antibiotic therapy. It is vital to target antibiotic therapy appropriately, and knowledge of the patient's airway microbiology can assist with this. Certain infective and colonising organisms, such as *Pseudomonas aeruginosa*, cause worse patient outcomes and so need prompt treatment with appropriate antibiotics. In addition to this general management approach, there are many different underlying causes of bronchiectasis that should be identified wherever possible, to support more targeted therapy and prevent disease progression.

This article provides a guide to the key principles of diagnosing and managing bronchiectasis, and outlines situations where more specialist respiratory support is required.

Key words: Bronchiectasis; Pseudomonas; Respiratory

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Introduction

Bronchiectasis is a common respiratory condition, with more than 200 000 people in the UK living with the disease (Snell et al, 2019). It is a chronic condition characterised by abnormal dilatation of bronchi. The recognised causes of this airway damage are wide and include prior respiratory infections, disorders of the immune system, co-existing lung conditions such as chronic obstructive pulmonary disease, and multisystem diseases such as rheumatoid arthritis. However, for many patients, no cause is established and, as such, it is labelled idiopathic. The structural dilatation of the airways impairs mucociliary clearance and frequently leads to sputum retention, chronic infection and inflammation, which further perpetuates the process (Cole, 1986). This can be recognised by the classic clinical phenotype of chronic productive cough and prescription of repeated courses of antibiotics to treat lower respiratory tract infections (King et al, 2006). For other patients, symptoms are mild or even absent, with the diagnosis made incidentally on imaging performed for other reasons.

Despite bronchiectasis being common, patients can face unacceptable delays in diagnosis and initiation of appropriate treatment (Anwar et al, 2013). There can also be a failure of timely detection of acute deterioration in symptoms, referred to as pulmonary exacerbations, that can adversely affect quality of life. Many of these patients present to non-respiratory physicians for either initial diagnosis or subsequent management, so a working knowledge of the disease is essential. This article provides an overview of the diagnosis and management of patients with bronchiectasis, aimed at non-respiratory physicians.

When should bronchiectasis be suspected?

Recognition of the classical symptoms of chronic cough, sputum production and recurrent lower respiratory tract infection should prompt investigation for bronchiectasis. There may be additional symptoms, such as pleuritic chest pain, haemoptysis and lethargy, but these are not specific (McShane et al, 2013). Patients with other lung conditions, most commonly

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Table 1. Clinical features and abnormal investigations that may prompt investigation for bronchiectasis in patients with pre-existing lung disease	
Clinical features that may suggest bronchiectasis	Increasing daily sputum volume or increased chronic sputum viscosity
	Recurrent episode of respiratory infection
	Worsening or recurrent exacerbation of asthma or chronic obstructive pulmonary disease
	New haemoptysis
Findings on investigations that may suggest bronchiectasis	Evidence of new airway thickening or dilatation on chest X-ray
	Isolation of *Pseudomonas aeruginosa* or non-tuberculous mycobacterium in sputum
	Repeated growth of common organisms implicated in bronchiectasis such as *Haemophilus influenza*e and *Staphylococcus aureu*s
	Evidence of aspergillus-related lung disease on serology, eg allergic bronchopulmonary aspergillosis

chronic obstructive pulmonary disease and asthma, can develop co-existent bronchiectasis (Quint et al, 2016). It can also develop in patients with other chronic medical conditions such as rheumatoid arthritis and inflammatory bowel disease. In these patients, a change in baseline clinical features should prompt further investigation (Table 1). In other cases, the diagnosis can first be suspected when pathogenic organisms, such as *Pseudomonas aeruginosa,* are identified in sputum samples. Last, bronchiectasis can be diagnosed in asymptomatic patients when identified incidentally on imaging performed for other purposes.

Confirming the diagnosis

The diagnosis is confirmed using high-resolution computed tomography of the lungs. The main radiological feature of bronchiectasis is bronchial dilatation (Figure 1). Patterns of bronchiectasis can be described radiologically as either cylindrical, varicose or cystic.

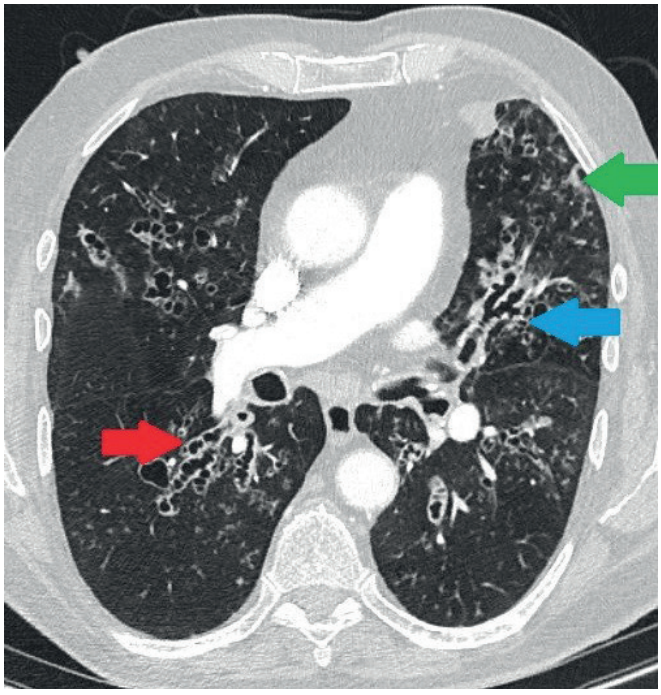

Figure 1. Computed tomography image from a patient with significant bronchiectasis. Significant cystic and varicose bronchiectasis is seen with bronchial wall thickening (red arrow), marked bronchial dilatation with lack of airway tapering (blue arrow) and areas of distal mucous plugging (green arrow).

There can also be bronchial wall thickening and mucous impaction. The distribution of the bronchiectasis, as well as presence of other abnormalities such as nodules or cavities, can be suggestive of the underlying cause of the bronchiectasis, or of complications such as atypical infection.

Approach to treating bronchiectasis

Management of symptomatic bronchiectasis is directed at interrupting the cycle of inflammation and infection via a stepwise approach (Figure 2). Many of these interventions are simple and can be performed outside of the specialist setting

Identify and treat underlying causes

All patients with bronchiectasis require investigation to try and identify an underlying cause. Many cases are labelled idiopathic or are attributed to structural damage sustained during a previous respiratory tract infection (post-infective). However, in cases where an underlying condition is identified, management can be changed (Gao et al, 2016). For most patients, this can be achieved with a small number of simple investigations (Table 2). In specific circumstances, such as presentation at a younger age or strong suspicion of primary immunodeficiency, a more comprehensive evaluation may be required.

Immune dysfunction is one of the most important causes of bronchiectasis to identify and is often the result of impaired antibody production (Gao et al, 2016). The presence of defects in antibody production is suggested by reduced levels of serum immunoglobulins, or by failure to mount an adequate antibody response to vaccination. Assessing vaccine responses is best undertaken in a specialist clinic and involves determining if there has been a significant change in antibody levels following vaccination. Patients with bronchiectasis who have previously had the pneumococcal vaccination (eg patients >65 years old via the NHS vaccination programme) should have their pneumococcal serology checked. If there has been an inadequate response, defined by inadequate antibody levels to <50% of pneumococcal serotypes, the authors' practice is to refer onwards to an immunologist (Paris and Sorensen, 2007). If there has been no prior history of pneumococcal vaccination, vaccination should be undertaken and then pneumococcal serology should be checked 4–6 weeks later to assess the immunological response.

In patients where immunodeficiency is suspected, either on initial testing or from the clinical history, the cause needs to be established. Some cases can be attributed to

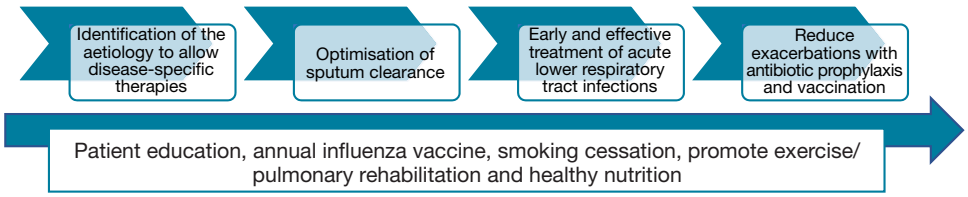

Figure 2. Stepwise approach to the initial investigation and management of new diagnoses of bronchiectasis. Adapted from Hill et al (2019).

Table 2. Proposed initial investigations for causes of bronchiectasis

Cause of bronchiectasis	Suggested investigation
Primary and secondary immunodeficiency	Immunoglobulins
	Serum electrophoresis
	Full blood count
Allergic bronchopulmonary aspergillosis	Total IgE
	Aspergillus-specific IgG and IgE
Non-tuberculous mycobacterium infection	Sputum culture

Adapted from Hill et al (2019)

the effects on the immune system of medications or medical conditions, such as human immunodeficiency virus infection, haematological malignancy or advanced age. In those with a primary immunodeficiency or where the cause remains unclear, referral to an immunologist is required. These patients may need specific therapies, including intravenous immunoglobulin replacement. Patients with primary immunodeficiency and co-existent bronchiectasis who receive immunoglobulin replacement have similar infective exacerbation rates and mortality to those with normal immune function (Goussault et al, 2019).

All patients should be tested for allergic bronchopulmonary aspergillosis and non-tuberculous mycobacterial lung disease. Both conditions can cause bronchiectasis, or be responsible for deterioration in patients with a pre-existing diagnosis. Allergic bronchopulmonary aspergillosis occurs as a consequence of a disordered allergic response to *Aspergillus fumigatus* colonisation of the airways. It should be suspected when there are raised levels of total IgE and *A. fumigatus*-specific IgE. The diagnosis is made with a combination of clinical features, radiology and serology findings, with treatment comprising a combination of corticosteroids and antifungal medication (Agarwal et al, 2013). Non-tuberculous mycobacteria are a group of environmental mycobacteria, some of which cause lung disease. The most common species causing lung disease is the *Mycobacterium avium* complex (Hoefsloot et al, 2013). If non-tuberculous mycobacterial disease is suspected, patients should be screened with a minimum of three sputum samples taken on different days. If they are not productive of sputum, induced sputum or bronchoscopy and bronchoalveolar lavage should be performed. The decision to treat requires at least two isolations in sputum or a single isolation on a bronchoalveolar lavage, alongside consistent radiological and clinical findings (Haworth et al, 2017).

Cystic fibrosis is an important cause of bronchiectasis. Most cases are picked up via newborn screening and in early childhood, so diagnosis in adults is rare (Hunt and Geddes, 1985). Investigations, such as sweat chloride test or genetic testing, may be considered in younger patients often with lifelong symptoms, an upper lobe predominant radiological pattern, and evidence of multisystem involvement, such as infertility or malabsorption (National Institute for Health and Care Excellence, 2017).

Primary ciliary dyskinesia is a genetic disorder of altered ciliary function and impaired mucociliary clearance (Lucas et al, 2017). Investigation for primary ciliary dyskinesia should be considered if there are clinical features including a neonatal history, situs invertus, chronic rhinosinusitis, congenital heart defects or chronic otitis media (Lucas et al, 2017). Suspected patients should be referred to specialist centres.

Other investigations can be considered, dependent on history and investigations. In patients with localised disease and no obvious cause, bronchoscopy can rule out endobronchial obstruction caused by tumour, external compression or foreign body. Where there are concerns about recurrent aspiration or gastro-oesophageal reflux, swallowing assessments may be appropriate. Other systemic conditions associated with bronchiectasis include rheumatoid arthritis, inflammatory bowel disease and alpha-1 antitrypsin deficiency.

Establishing a sputum clearance regimen

The accumulation of sputum within the respiratory tract propagates the vicious cycle of inflammation and chronic infection in bronchiectasis (Cole, 1986). As such, effective strategies to clear sputum play a pivotal role in the long-term management of bronchiectasis (Murray et al, 2009). All patients require a personalised airway clearance strategy that is taught by a respiratory specialist physiotherapist. There are a number of methods available, but most UK centres prefer the active cycle of breathing technique (Hill et al, 2019). However, the eventual choice of technique takes account of patient-specific factors, such as lung disease characteristics, as well as likely compliance with a proposed technique (O'Neill et al, 2019). It is critical is to recognise when the current strategy is insufficient and reassess.

If airway clearance techniques do not lead to sufficient sputum expectoration, use of mucolytic medications may prove helpful. In line with British Thoracic Society guidance,

the authors' practice is to use nebulised hypertonic saline in combination with airway clearance techniques (Hill et al, 2019). Hypertonic saline may reduce exacerbation frequency, as well as improving quality of life and lung function (Kellett and Robert, 2011). Oral mucolytics, such as carbocisteine, are frequently prescribed, despite limited evidence to support their use (Wilkinson et al, 2014). From the authors' experience, they do play a role, especially in patients not able to tolerate hypertonic saline.

Lifestyle advice

Promoting healthy lifestyles alongside medical therapy is an important part of managing all chronic diseases. Smoking cessation should be recommended to all current smokers. Exercise should be promoted for all patients. Any patient who is limited by breathlessness should be considered for pulmonary rehabilitation. It provides short-term benefits in exercise tolerance and health-related quality of life (Zanini et al, 2015). Those with severe airflow obstruction and those experiencing two or more exacerbations per year are most likely to derive benefit (Zanini et al, 2015; Lee et al, 2017).

Maintaining a healthy weight is important. Low body mass index is associated with increased rate of exacerbations, increased mobility, increased rates of *Pseudomonas* colonisation, decreased exercise tolerance, increased hospitalisation rates and death (Qi et al, 2015). Dieticians should be involved locally when there are concerns regarding a patient's nutritional state.

Managing acute exacerbations

During an acute exacerbation, sputum can become more purulent, thicker and increase in volume. There may also be breathlessness, fatigue or haemoptysis (Hill et al, 2017). Patients can describe different time frames for an exacerbation, some presenting acutely with rapid deterioration over a period of days, whereas others present more insidiously over weeks to months. The pathology of exacerbations is poorly understood (Amati et al, 2019), but the principal management is antibiotics. Antibiotic selection is based on several considerations, such as previous sputum culture results, local microbiology resistance patterns and the patient's response to previous antibiotic agents. A course of antibiotics should be given for between 10 and 14 days (Hill et al, 2019). Sputum sampling at the start of therapy is recommended to guide second-line agents in those not responding.

Many patients will have their own self-management plan for managing exacerbations, detailing how they should manage sputum clearance and when they should seek further medical attention if they are deteriorating.

In some situations, intravenous antibiotics are required to treat exacerbations. This can occur when there is a failure to respond to oral antibiotics, in patients who require hospital admission, or in those with a sputum isolate that is not sensitive to a suitable oral agent. Intravenous antibiotics should be administered in the outpatient setting when available, but patients need careful monitoring and oversight by a dedicated team. In addition, patients may need to escalate airway clearance by increasing the frequency or changing mucolytic regimen. In those with co-existent chronic obstructive pulmonary disease or asthma, bronchodilators and steroids may be prescribed. In severe exacerbations, admission to hospital may be required.

New isolation of *Pseudomonas aeruginosa*

Pseudomonas aeruginosa is a Gram-negative bacteria that can colonise the airways in patients with bronchiectasis. Compared to patients without *P. aeruginosa,* its presence is associated with worse outcomes, including increased mortality, greater rates of pulmonary exacerbation and worse quality of life (Finch et al, 2015). A retrospective observational study suggested that successful eradication of *P. aeruginosa* is associated with improvements in mortality and exacerbation frequency (White et al, 2012). To treat newly detected *P. aeruginosa,* the authors' practice, in line with national guidance, is to use oral ciprofloxacin (750 mg twice daily) as first-line therapy; if this is unsuccessful a combination of 2 weeks of appropriate intravenous antibiotics and 3 months of nebulised antibiotics, most often colistin two million units twice daily, is used (Hill et al, 2019).

Additional therapies to reduce exacerbation frequency

In bronchiectasis, the exacerbation frequency predicts risk of death, hospital admission, frequency of exacerbation and quality of life; patients with four or more exacerbations in the previous year have the worst outcomes (Chalmers et al, 2014). As such, patients with recurrent exacerbations require aggressive management to reduce the frequency. In patients who have had airway clearance optimised and other possible contributing factors excluded, such as new isolation of *P. aeruginosa* or mycobacterial pathogen, long-term antibiotics can be considered.

British Thoracic Society guidance recommends that the initial form of prophylaxis should be determined by whether the patient is chronically colonised by *P. aeruginosa* (Hill et al, 2019). Patients with *P. aeruginosa* should receive regular nebulised colistin, whereas those without *P. aeruginosa* colonisation should receive regular oral macrolide antibiotic therapy.

Chalmers et al (2019) suggested that regular macrolide therapy (such as azithromycin) also significantly reduces the risk of exacerbations in bronchiectasis patients colonised with *P. aeruginosa*. As such, the authors' practice is for an initial trial of a macrolide in all patients, as long as there are no contraindications. This approach has the advantage of reducing delays in starting therapy, as well as being less time consuming for the patient than nebulised antibiotics. Before commencing nebulised antibiotics, patients require a supervised test with spirometry to ensure the medication is tolerated and does not provoke bronchospasm. Depending on availabilities of local services, this can lead to delays. The authors' recommended pathway is shown in Figure 3.

The exact mechanism of the efficacy of macrolides in patients with bronchiectasis is not clear. It is believed to go beyond the drug's antimicrobial properties and may have direct effects on reducing airway inflammation (Kanoh and Rubin, 2010). Patients commencing macrolides should be counselled regarding symptoms of ototoxicity, have a baseline electrocardiogram to assess the QT interval, regular liver function blood monitoring and should have at least one negative sputum culture for non-tuberculous mycobacteria. Sputum surveillance for non-tuberculous mycobacteria should be performed annually in patients on long-term macrolides.

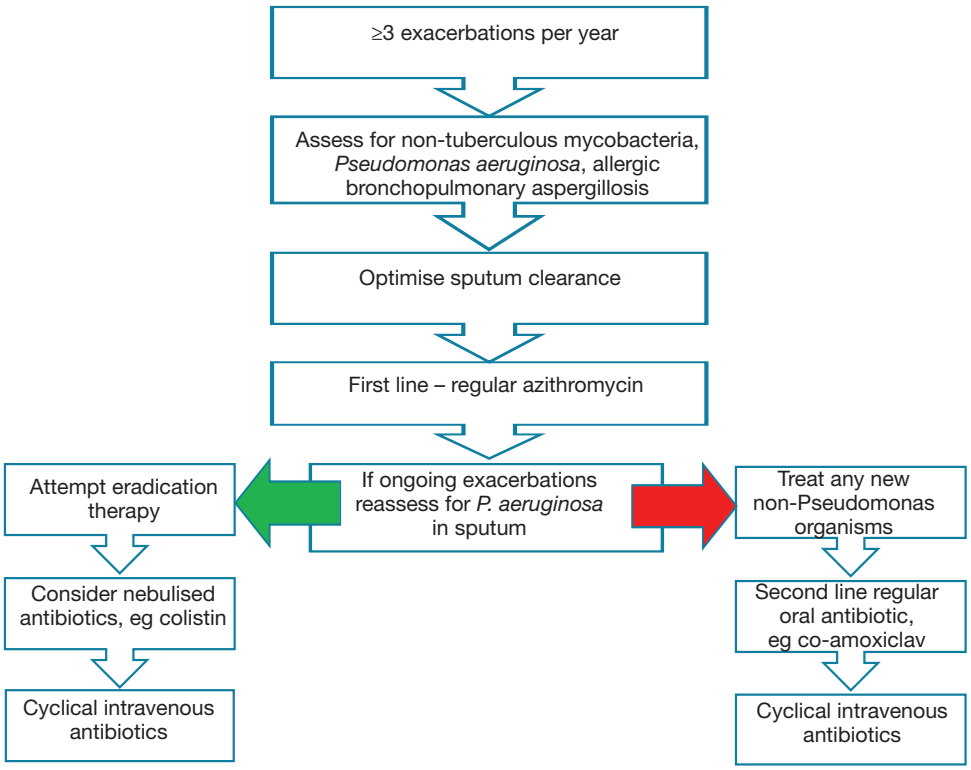

Figure 3. Stepwise approach to the use of long-term antimicrobial therapies in patients with frequent exacerbations.

Patients whose exacerbation frequency does not reduce despite the above measures should be under the care of specialist bronchiectasis services. Subsequent management is largely determined by the colonising organism. The authors' service trials other regular oral antibiotics such as co-amoxiclav and doxycycline. It is important to review the sputum microbiology and make decisions on alternative agents based on organisms identified, patterns of resistance, and patient allergies and drug intolerances. In more severe cases other strategies can be trialled, such as the use of alternative nebulised agents and regular planned courses of intravenous antibiotics.

Inhaled bronchodilators and corticosteroids

There is no evidence to support the routine use of bronchodilators or inhaled corticosteroids in patients with bronchiectasis. However, obstructive patterns of spirometry are frequently seen within this population. This can be a result of the small airway obstruction seen in bronchiectasis, or a result of co-existent asthma or chronic obstructive pulmonary disease (Quint et al, 2016). Where there is clinical evidence to support a co-existing diagnosis of asthma or chronic obstructive pulmonary disease, treatment should be as per national guidance for these conditions.

End-stage disease

Many patients with bronchiectasis with end-stage disease will be under the care of a respiratory physician. A small proportion of patients may be suitable for transplantation, with one UK centre suggesting 6% of lung transplants are performed to treat non-cystic fibrosis bronchiectasis (Birch et al, 2018). However, this represents a very small proportion of patients, and many more may benefit from management of chronic respiratory failure, eg long-term oxygen therapy or ventilation. Early engagement with community palliative care services may be indicated in such patients, and its importance should not be overlooked.

When do patients require referral?

Most patients do not require regular follow up under a respiratory physician, but those who may require further assessment or ongoing management are listed in Table 3. Referrals from general practice are appropriate to help establish the diagnosis, using computed tomography, and for establishing a clear management plan and physiotherapy regimen. Once in place, most patients can be adequately managed back in primary care.

Conclusions

The management of patients with bronchiectasis is multi-faceted and, with the associated morbidity, mortality and frequent exacerbation rate, it is likely that many will present acutely to hospital or be identified in other clinical situations. A knowledge of the aetiology, the

Table 3. British Thoracic Society suggested criteria for specialist respiratory follow up

Sputum samples culturing *Pseudomonas aeruginosa*, non-tuberculous mycobacteria or meticillin-resistant *Staphylococcus aureus*
Deteriorating lung function
Recurrent exacerbations (at least three per year)
Patients on long-term antibiotics (nebulised or intravenous)
Associated with rheumatoid arthritis, immune deficiency, inflammatory bowel disease and primary ciliary dyskinesia
Allergic bronchopulmonary pulmonary aspergillosis
Advanced disease and considering lung transplantation

Adapted from Hill et al (2019)

Key points

- The effective management of patients with bronchiectasis should be tailored to each patient.
- Where possible, an underlying aetiology should be identified and treated to prevent disease progression.
- Patients should undergo assessment for sputum clearance and exacerbations should be treated promptly and guided by both present and historical sputum culture results.
- Patients with frequent exacerbations should be considered for long-term antimicrobial therapy.
- Those with worsening symptoms despite optimal treatment should be assessed for the development of complications, for example colonisation with *Pseudomonas*, and should be referred to specialist respiratory services.

patient's exacerbation history and sputum microbiology is essential in formulating immediate management plans, at times where there may not be specialist respiratory support available. With the prevalence appearing to be increasing in the UK, those working in acute medical specialties need a basic understanding of the disease, should be able to implement initial investigation and management and should appreciate which patients require prompt referral to specialist respiratory services.

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