Chapter 4

Assessment and investigation of adults with bronchiectasis

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Summary

The diagnosis of bronchiectasis is made on the basis of high-resolution computed tomography (HRCT) scan findings. A diagnosis of bronchiectasis should be considered in all patients with persistent cough productive of sputum, where another clear diagnosis has not been made. This includes patients with an initial diagnosis of chronic obstructive pulmonary disease or severe asthma. Once bronchiectasis has been confirmed by HRCT scanning, patients should undergo a range of investigations to determine whether or not there is an underlying cause. This can usually be determined in approximately 50% of patients with bronchiectasis. The common conditions which should be sought are cystic fibrosis, immunodeficiency syndromes, primary ciliary dyskinesia, and autoimmune diseases, such as rheumatoid arthritis and ulcerative colitis. For many of these conditions, there is specific treatment to improve symptoms and reduce lung injury but, without an accurate diagnosis, appropriate therapy may not be instituted.

Keywords: Bronchiectasis, computed tomography scan, cystic fibrosis, primary ciliary dyskinesia, primary immunodeficiency

Bronchiectasis is a generic diagnostic term that describes the pathological dilation of the airways found in a number of chronic lung conditions. The aetiology of bronchiectasis is varied (table 1), and, in most series, an underlying cause can only be definitively identified in 50% of cases [1, 2]. The importance of determining a cause lies in facilitating treatment that may improve symptoms, reduce exacerbations and alter the course of the disease by preserving lung function. In one series in children, extensive investigation detected a specific cause in 74% of those investigated, and this led to a change in treatment in 56% [3]. In an adult series from the same geographical area, a diagnosis was again reached in 74%, and the treatment of 37% of these was affected by knowledge of the diagnosis [4].
Childhood respiratory infection, e.g. whooping cough, measles, tuberculosis (TB) or severe bacterial pneumonia, is cited as being responsible for a large proportion of cases of bronchiectasis, i.e. up to 50% [4–6]. This potential cause, however, is subject to recall bias, particularly since the majority of cases present in the fifth and sixth decades of life. Many people of this age have had measles, whooping cough or other childhood infections associated with respiratory infection, including pneumonia. In addition, the first episode of pulmonary infection could represent the first exacerbation of bronchiectasis. Bronchiectasis is found in association with numerous multisystemic diseases, such as cystic fibrosis (CF) [7], immunodeficiencies [8], α1-antitrypsin (α1-AT) deficiency [9], primary ciliary dyskinesia (PCD) [10], rheumatoid arthritis and inflammatory bowel diseases, especially ulcerative colitis [1, 7, 11].

Prevalence

The prevalence of bronchiectasis is almost certainly underestimated. This is because it is a condition that many healthcare practitioners are unfamiliar with, and it is frequently misdiagnosed as asthma or chronic obstructive pulmonary disease (COPD) due to the similarities in clinical findings (table 2).

In the USA, the prevalence of bronchiectasis has been estimated at 4.2 per 100,000 population among those aged 18–34 years, rising to 272 per 100,000 population in those aged >75 years [12].
However, these values are derived from a database of claims from 30 different healthcare insurance plans made over a 2-year period. They are likely to underestimate the true prevalence as they exclude not only the uninsured population but also those who use alternative plans. It cannot, therefore, be claimed that they are truly representative of the real population prevalence. The prevalence of non-CF bronchiectasis in Northern Ireland is estimated at around 5,000 in a population of approximately 2 million [13], leading to 300–400 admissions per annum for the treatment of an infective exacerbation.

In children, bronchiectasis is less common. It can be extrapolated that the prevalence should be falling following the advent of improved antibiotic therapies and vaccination of children during the first year of life. Only two national studies have been reported with very different rates, 0.5 per 100,000 population in Finland [14] and 3.7 per 100,000 population in New Zealand [15]. In certain indigenous population groups, the prevalence is much higher, e.g. the New Zealand figure doubles among the Maori and Pacific Islander populations [11, 15], Aboriginal rural communities have 14.7 per 1,000 population affected among those aged <16 years [16] and 16 per 1,000 population in Alaskan natives [17]. This is thought to occur due to an increased rate of severe pulmonary infection in early childhood, due to a combination of socioeconomic factors rather than solely a genetic predisposition.

### Approach to diagnosis

The diagnostic approach to a patient with bronchiectasis should first establish that there is radiological evidence of airways dilatation and secondarily consider possible underlying conditions [1].

<p>| Table 2. Clinical findings in chronic obstructive pulmonary disease (COPD), asthma and bronchiectasis |</p>
<table>
<thead>
<tr>
<th>COPD</th>
<th>Bronchiectasis</th>
<th>Asthma</th>
</tr>
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<tbody>
<tr>
<td><strong>Symptom</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Sputum production</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>++</td>
<td>+/-</td>
</tr>
<tr>
<td>Wheeze</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Haemoptysis</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Fever</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Lethargy</td>
<td>+/-</td>
<td>+</td>
</tr>
<tr>
<td>Recurrent infection</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>Clinical signs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Finger clubbing</td>
<td>No</td>
<td>Extensive disease</td>
</tr>
<tr>
<td>Breath sounds</td>
<td>↓/wheeze</td>
<td>Normal/ ↓</td>
</tr>
<tr>
<td>Added sounds</td>
<td>Wheeze</td>
<td>Crackles</td>
</tr>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spirometry</td>
<td>FEV1 ↓, FVC ↓, FEV1/FVC ↓</td>
<td>FEV1 ↓/normal FVC ↓/normal</td>
</tr>
<tr>
<td>Reversibility</td>
<td>15%</td>
<td>40%</td>
</tr>
<tr>
<td>Lung volumes</td>
<td>↓/↑</td>
<td>Normal/ ↓</td>
</tr>
<tr>
<td>Transfer factor</td>
<td>Normal</td>
<td>Normal/ ↓</td>
</tr>
<tr>
<td>Hypoxia</td>
<td>Yes</td>
<td>Yes/no</td>
</tr>
<tr>
<td><strong>Radiology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chest radiography</td>
<td>Chronic inflammatory changes, hyperinflation</td>
<td>Tramlines, ring shadows/normal</td>
</tr>
<tr>
<td>CT findings</td>
<td>Hyperinflation, air-trapping, bullae, may have mildly dilated airways or thickened bronchial wall</td>
<td>Dilated bronchi, thickened bronchial wall, lack of tapering of bronchi, bronchi visible in outer 1–2 cm, air-trapping</td>
</tr>
</tbody>
</table>

CT: computed tomography; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; -: uncommon; +/-: occurs sometimes; +: common; ++: very common; ↓: decrease; ↑: increase.
People presenting with a chronic productive cough lasting for >4 weeks or recurrent episodes, with two or more episodes occurring over 8 weeks, should have the diagnosis of bronchiectasis considered [2]. In the scheme outlined in figure 1, all of the first-line investigations should be considered as routine in patients being investigated for bronchiectasis. Most people have already undergone some investigations prior to referral, such as a sputum culture, chest radiography or computed tomography (CT), which may guide further investigations.

**Symptoms and physical findings**

Cough productive of sputum is the most common symptom associated with bronchiectasis [1, 18–21]. In some studies, 25% of patients do not report excessive daily sputum production, but describe a marked increase in volume during an exacerbation [1, 18]. Occasional haemoptysis is a frequent symptom and is reported by half of all patients. This is often associated with a pulmonary exacerbation. Shortness of breath, fever and chest pain are also common complaints among non-CF bronchiectasis patients [18], although they are common symptoms in other chronic inflammatory lung disease that may coexist, e.g. COPD and asthma (table 2). Patients presenting with such symptoms who do not respond as expected to usual therapy should raise the possibility of bronchiectasis and this should be investigated. Some symptoms point to specific diagnoses (table 3).

**Physical examination**

Physical findings are of modest help in the assessment of patients with bronchiectasis. The classic findings of wet crackles and finger clubbing are now uncommon and should trigger investigation for conditions associated with severe bronchiectasis, such as CF. Crackles with some associated

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**Figure 1.** Diagnostic approach to bronchiectasis. HRCT: high-resolution computed tomography; [Cl]: chloride ion concentration; CF: cystic fibrosis; Ig: immunoglobulin; α₁-AT: α₁-antitrypsin; PCD: primary ciliary dyskinesia; NO: nitric oxide; RF: rheumatoid factor; CTD: connective tissue disease; ABPA: allergic bronchopulmonary aspergillosis; PD: potential difference; EM: electron microscopy; CVID: common variable immunodeficiency.
wheeze are the most common findings, with finger clubbing now a rare feature, and usually associated with severe disease. Other aspects of examination should focus on clinical signs of associated diseases, such as CF, immune deficiency or a connective tissue disease.

### Diagnostic tests

#### Blood tests

A complete blood count, although nonspecific, is important in monitoring the ongoing condition of each individual patient. Haemoglobin level can be low secondary to anaemia of chronic disease, and, conversely, patients may be polycythaemic secondary to chronic hypoxia. An elevated white cell count may indicate the presence of acute infection. The differential white cell count can reveal lymphopenia, which may prompt further investigation for immunodeficiency syndromes or eosinophilia, which can occur in but is not diagnostic of allergic bronchopulmonary aspergillosis (ABPA).

C-reactive protein (CRP) is an acute-phase reactant commonly measured in respiratory patients with acute exacerbations in order to assist in determining whether or not there is a systemic inflammatory response [1, 22, 23]. In bronchiectasis patients in a stable state, it has been shown that CRP levels are elevated from baseline [22]. The CRP level also correlated with decline in lung function and severity of disease on high-resolution CT (HRCT) in the same series [22].

#### Radiology

Although suspected with a history of recurrent lower respiratory tract infection on a background of chronic cough and sputum production, the diagnosis of bronchiectasis can only be confirmed radiologically [2]. The gold-standard investigation is HRCT. This was first described in 1982 [16], and permits a detailed examination of the lung architecture using a noninvasive technique. Historically, the diagnosis was based on bronchography, which involved instillation of a radiopaque dye into the airways and fluoroscopic screening. This technique has been superseded due to the greater detail available in a safer more easily tolerated imaging method and is now obsolete.

Volumetric HRCT has some advantages over conventional HRCT as it provides more-detailed images, but it is more prone to image degradation due to motion artefact and requires a higher radiation dose. Standard HRCT is appropriate for the majority of patients.

Findings on HRCT are bronchial wall thickening with dilatation of the bronchi to a diameter greater than that of the accompanying arteriole (the signet-ring sign); lack of normal tapering of bronchi/bronchioles on sequential slices; and visualisation of bronchi in the outer 1–2 cm (fig. 2) [1, 23, 24]. The bronchiectatic changes in CF have been quantified using a number of scoring systems, but the value of these in diagnosis or follow-up care has not been established.

The histopathological appearance of bronchiectasis has been further subcategorised as cylindrical, saccular and varicose, depending on the shape of the bronchi [25]. The true clinical significance of these subdivisions is unclear. However, cystic bronchiectasis has been associated with an increased frequency of exacerbation and more-clinically significant disease [24]. HRCT appearance can also be used to confirm any other parenchymal or bronchiolar pathology, such as interstitial lung
disease [25, 26]. The distribution of ectatic airways throughout the lung fields can be used to guide investigation of underlying causes, but most changes are nonspecific (table 4) [27, 28].

Although the diagnosis is confirmed radiologically using HRCT, a posteroanterior chest radiograph should be obtained as a baseline with which to compare future films in the event of acute exacerbation. Depending on the distribution of the bronchiectasis and the degree of damage, the chest radiograph may show minimal change from normal or be markedly abnormal. Traditionally, the radiographic changes associated with bronchiectasis are tramlines and ring shadows [18]; these markings correspond to the thickened mucosa of the more-severely inflamed airways in transverse or cross-section.

**Table 4.** High-resolution computed tomography features of bronchiectasis

<table>
<thead>
<tr>
<th>General features</th>
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<tbody>
<tr>
<td>Bronchial dilatation (bronchus diameter greater than that of adjacent vessel)</td>
</tr>
<tr>
<td>Bronchial wall thickening</td>
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<tr>
<td>Bronchial plugging</td>
</tr>
<tr>
<td>Areas of reduced attenuation (mosaic pattern)</td>
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<table>
<thead>
<tr>
<th>Specific features</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABPA: upper-zone central bronchiectasis</td>
</tr>
<tr>
<td>Cystic fibrosis: upper-zone bronchiectasis</td>
</tr>
<tr>
<td>NTM/MAC: Middle-lobe irregular branching and tree-in-bud appearance</td>
</tr>
</tbody>
</table>

ABPA: allergic bronchopulmonary aspergillosis; NTM: nontuberculous mycobacteria; MAC: *Mycobacterium avium-intracellulare* complex.
Once the diagnosis of bronchiectasis has been confirmed, a detailed clinical work-up should be undertaken in order to determine the extent of the impact on lung function, morbidity and prognosis, the underlying cause of the existing structural lung damage and the most prevalent infecting organisms. The benefits of this are that not only can treatment be tailored to the individual, but also a potentially treatable underlying condition may be uncovered [1, 24, 25].

A comprehensive clinical assessment, including a detailed history and physical examination, are required to illicit any pointers towards a specific diagnosis. This should be followed up by extensive investigation to allow determination of baseline functional status and lung function and to permit guidance of treatment. During the course of investigation, underlying conditions which are known to have an association with bronchiectasis, albeit not a causative one, may be discovered.

**Pulmonary function testing and other physiological factors**

Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) should be measured at the time of the diagnostic evaluation and at least annually, more frequently in the setting of PCD, immunodeficiency or connective tissue disease [21, 24]. Spirometric results may be normal in some patients, although usually show a pattern of airflow limitation, with a decreased FEV1 and a reduced FEV1/FVC ratio. FVC may be normal or slightly reduced, although this finding alone may be indicative of mucous impaction [2, 24]. Airway hyperresponsiveness has also been demonstrated. In 40% of patients, an FEV1 reversibility of >15% following administration of β-agonist can be demonstrated [29]. In addition, 30–69% of patients who do not exhibit a reduced FEV1 at baseline, show a 20% decrease in FEV1 following histamine or methacholine challenge [30, 31], indicating clinically significant hyperresponsiveness. FEV1 has the strongest correlation with severity of structural abnormality on HRCT [32, 33]; however, it correlates poorly with clinical fluctuations in disease course.

Full pulmonary function testing, including lung volumes and gas transfer coefficient, should be carried out at the outset in adult presentations in order to give a picture of the overall functional status of the lungs and also to assist in the diagnosis of underlying conditions [2]. Reduced lung volumes and transfer factor should prompt consideration of underlying interstitial lung disease. Elevated lung volumes can be secondary to air-trapping or indicate mucous impaction of small-calibre airways.

Exercise testing, such as the incremental shuttle test and 6-minute walking test, are widely used tools for the assessment of functional capacity in chronic pulmonary disease patients and can be applied to bronchiectatic patients [34]. However, such tests have no value in diagnosis and there are no data to support their use outside of clinical studies [35]. Limitation of exercise capacity has not been shown to correlate with severity of airway damage on HRCT [36].

Studies in post-resection patients have shown that exercise testing is more informative as an ongoing assessment of lung function than static spirometry, particularly in patients whose performance or symptoms do not correlate with spirometric results [37].

**Specific investigations**

**Cystic fibrosis**

CF is the single most common cause of structural bronchiectasis in children and a reasonably common diagnosis in adults [2, 7, 24]. Increasingly, CF is diagnosed later in life, with many patients now being diagnosed in their third and fourth decades of life, and some even later [38–43]. Given this, all adults presenting with bronchiectasis and other features of CF should undergo comprehensive investigation in order to rule out CF. Pilocarpine iontophoresis for sweat chloride ion concentration ([Cl−]) measurement, should be carried out in all patients with bronchiectasis and a clinical suspicion of CF [2, 44]. The results should be interpreted as detailed in table 5. A sweat [Cl−]
of <30 mM effectively excludes CF as a diagnosis, although one CF-disease-causing mutation has been described with normal sweat [Cl] [44]. If the sweat [Cl] is >60 mM, a diagnosis of CF is confirmed. If the sweat test result is 30–60 mM, the identification of one or more disease-causing mutations determines which diagnostic category the patient falls into, CF or CF transmembrane conductance regulator (CFTR)-related disorder (table 5) [44]. The diagnostic category of CFTR-related disorder has recently emerged and describes single-organ disease, most frequently bronchiectasis, with an associated sweat [Cl] of 30–60 mM or one or two disease-causing mutations of the CFTR. In some cases of diagnostic uncertainty, measurement of nasal potential difference may help to determine CFTR dysfunction. This may help to distinguish CF from a CFTR-related disorder [44].

Immunological investigations

A range of immunological abnormalities are associated with non-CF bronchiectasis [24]. The prevalence of each in bronchiectasis varies from study to study. Humoral immunity can be affected by low levels of any of the major immunoglobulin (Ig) classes, IgM, IgG and IgA [1, 24, 45, 46]), and, in some cases, IgG subclasses, IgG1, IgG2, IgG3 and IgG4. The specific antibody response to polysaccharide and peptide vaccines provides additional information about the innate immune response to antigenic stimulus [11].

Specific IgG subclass deficiency can be detected in serum or by checking the antibody response to vaccination with either pneumococcal or Haemophilus influenzae and tetanus toxoid vaccines. This is performed by measuring antibody levels prior to administration of a dose and again 4 weeks later in order to investigate whether or not the individual has mounted an appropriate response [45]. Specific antibody response studies should be undertaken in consultation with an immunologist as interpretation of responses is complex, and a decision to treat patients with specific deficiencies with Ig replacement requires a range of considerations and should undertaken by an immunologist with expertise in this area [2]. Replacing deficient IgG is usually effective in reducing the frequency of infection and preventing further lung damage [45–47]. Neutrophil, T-cell, B-cell and complement disorders are a rare cause of bronchiectasis, and functional studies should be discussed with a specialist immunologist. All patients with an identified immunodeficiency should be managed with a specialist immunologist [2].

Primary ciliary dyskinesia

PCD is an autosomal recessive disorder leading to immotile cilia, and occurs in 1 in 15,000 to 1 in 40,000 of the population. It results in bronchiectasis and sinusitis and, in around half of cases, Kartagener’s syndrome (bronchiectasis, sinusitis and situs inversus) [10]. Diagnosis is based on exhaled nasal nitric oxide levels and electron microscopy of nasal biopsy specimens [48]. Reduced nitric oxide level has a specificity of 98% and a positive predictive value of 92% for PCD [48], and may be used as a screening tool to select those in whom nasal mucosal biopsy for electron microscopy is required. The diagnostic gold standard is transmission electron microscopy of nasal biopsy specimens to view the ultrastructural defects in the dynein arms within individual cilia [10]. Recent studies suggest that 15% of patients with functional PCD show no ultrastructural defects and so there is a high false-negative diagnostic rate [10]. Genetic testing is now becoming more readily available and may go some way towards overcoming limitations to ultrastructure as a diagnostic method [10].

| Table 5. Sweat test diagnostic criteria for cystic fibrosis (CF) |
|-----------------|--------------------------------------------------|
| Sweat [Cl] mM   | Diagnostic conclusion                           |
| ≥60             | CF confirmed                                    |
| 30–60           | Equivocal: further investigation required: CFTR DNA test |
| ≤30             | Not CF                                          |

[Cl]: chloride ion concentration; CFTR: CF transmembrane conductance regulator.
Allergic bronchopulmonary aspergillosis

IgE is a sensitive marker for ABPA if levels are $>1,000$ IU·L$^{-1}$. *Aspergillus* precipitins or specific IgG directed against *Aspergillus* confirm the diagnosis. This condition responds well to a combination of high-dose oral corticosteroid and oral antifungal therapy [2, 49–51].

$a_1$-Antitrypsin deficiency

In order to diagnose $a_1$-AT deficiency, serum levels of $a_1$-AT should be checked with the biochemical phenotype requested in those patients with low levels, particularly if there is a family history of respiratory disease of young onset, or in family members who have never smoked or show evidence of bullous disease on HRCT [9]. Genetic tests for the different genotypes (M, Z and S) are also now available.

Connective tissue disorders

Autoimmune disease covers a spectrum of conditions, which, although rare individually, can cause bronchiectasis and, depending on the condition, may respond to directed treatment. These conditions can be screened for by thorough history-taking and measurement of rheumatoid factor and other specific autoantibodies, such as antineutrophilic cytoplasmic antibody and cryoglobulin [2]. More common autoimmune conditions with a strong association with bronchiectasis are rheumatoid arthritis and ulcerative colitis. It is recommended that patients attending specialist rheumatology or gastroenterology clinics for monitoring of these conditions who develop chronic cough or respiratory symptoms should undergo lung function testing and HRCT in order to rule out bronchiectasis.

Gastro-oesophageal reflux

Gastro-oesophageal reflux disease has been associated with bronchiectasis, although it is unclear whether or not there is a direct causal relationship. If suspected, barium studies and fluoroscopy are indicated [2, 24].

Infection and sputum microbiology

Sputum microbiology is a key investigation in the diagnosis of patients with bronchiectasis [52]. *H. influenzae* is the most-frequently isolated pathogen, being found in up to 35% of patients. *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa* are also commonly identified organisms [53]. *Aspergillus* sp. may also be found, and may be related to a diagnosis of ABPA. The presence of *P. aeruginosa* in sputum from people with bronchiectasis is associated with more-severe lung disease and may also have a negative impact upon prognosis [54, 55].

Monitoring disease activity

Monitoring disease activity in bronchiectasis can be difficult as there is little fluctuation in lung function as measured by spirometry [2]. The inflammatory response to infection in bronchiectasis has been shown to be compartmentalised, with higher concentrations of inflammatory mediators being found in the airways than in the systemic circulation [3, 56].

Patients’ symptoms are a very important guide to pulmonary exacerbations, with increased cough, sputum volume and purulence, and haemoptysis and reduced energy all being common symptoms.

Sputum analysis plays a pivotal role in the assessment of bronchiectasis, with antibiotic therapy being directed by the results of sputum culture and antibiotic sensitivity testing. Sputum culture should be performed at all outpatient reviews and when symptoms deteriorate.
Although exacerbation rate does not clearly correlate with particular organisms, it has been shown to increase with increasing resistance of organisms to antibiotics [54]. Longitudinal studies demonstrate that subjects who carry the same organism after a 5-year period tend to carry increasingly resistant organisms, making exacerbations more difficult to treat successfully [54]. Recent studies using molecular identification techniques in the sputum of CF patients have revealed a wider spectrum of organisms in significant quantities than culture alone [57]. This has led to the discovery that the CF microbiome is much more extensive and diverse than was previously suspected. This is also likely to be the case in non-CF bronchiectasis. Molecular diagnostic methods are considerably more expensive than culture-based methods and not freely available in most clinical microbiological laboratory settings.

Exacerbations are often associated with new isolates of bacteria and respond to antibiotic therapies. However, in many such episodes, no clinically significant organism can be identified as the precipitating factor. Although it may be some time before molecular diagnostics enter clinical practice, it is worth bearing in mind, in the case of an infection not responding to standard antibiotic therapy, that there are other potentially pathogenic organisms present that may require alternative treatment. As a rule of thumb, sputum culture is more likely to underestimate the prevalence of bacterial infection, and each positive culture should be treated with appropriate antibiotics.

A thorough structured approach to the investigation of patients with suspected bronchiectasis will enable further learning about the natural history of the condition and improve patient outcomes by appropriate direction of treatment.

**Statement of interest**

None declared.

**References**