Pathogenesis and diagnosis of bronchiectasis

Educational aims

To describe the important factors involved in the pathogenesis of bronchiectasis.

To define how a diagnosis of bronchiectasis is made.

Summary

Bronchiectasis is an important cause of respiratory morbidity but one that has generally had a low profile. The prevalence of this condition varies but is common in certain indigenous populations and, anecdotally, in developing nations. It also has been recently recognised to be an ongoing problem in developed countries. As bronchiectasis is heterogeneous with a large number of predisposing factors and, generally, a long clinical history, the pathogenesis has not been well defined. The combination of a microbial insult and a defect in host defence allow the establishment of persistent bronchial infection and inflammation leading to progressive lung damage. Lung function testing usually demonstrates a mild to moderate obstructive pattern, which arises from inflammation in the small airways. There are a number of risk factors associated with this condition, which is commonly idiopathic. The microbiology of bronchiectasis is complex and changes as the disease progresses. The diagnosis is made by a combination of clinical symptoms and high-resolution computed tomography (HRCT) demonstrating abnormal airway dilatation.

Pathogenesis

Bronchiectasis is a heterogeneous condition with a large number of potential aetiological factors and, generally, a very long clinical history. The pathogenesis is not well understood but can be considered in different areas, which will be discussed below. In studies of adults, bronchiectasis is commonly idiopathic.

Epidemiology

The prevalence of bronchiectasis has not been defined. It was thought that the introduction of antibiotics would effectively mean that patients no longer developed bronchiectasis.

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and, as a consequence, there has been a low index of suspicion and underdiagnosis. The advent of HRCT scanning has made the diagnosis of bronchiectasis much easier and led to an increased awareness. EASTHAM et al. [3] reported a 10-fold increase in the rate of diagnosis of bronchiectasis with the use of HRCT.

A high prevalence has been described in certain indigenous populations, including Alaskan natives [4], New Zealand Maoris [5] and Australian aborigines [6]. These populations have a high level of social disadvantage and, in the aboriginal population, poor nutrition and access to healthcare.

Bronchiectasis is described as common in developing nations but there is a lack of data on the actual prevalence. TSANG and TIPOE [7] reported an incidence of 16.4 per 100,000 population in Hong Kong.

WEYCKER et al. [8] estimated that there were at least 110,000 adults in the USA with bronchiectasis. He described the bronchial wall to be infiltrated with inflammatory cells. Ciliated epithelium was often replaced with squamous or columnar epithelium. The elastin layer was deficient or absent and, in more severe cases, there was destruction of muscle and cartilage; these changes were responsible for bronchodilatation. He described three main forms of bronchiectasis: 1) follicular, 2) saccular and 3) atelectatic.

Follicular bronchiectasis was the most common form, and this corresponds to tubular or cylindrical bronchiectasis. The term follicular was used as this form was characterised by the presence of lymphoid follicles in the small airways and bronchioles. The major changes in this form of bronchiectasis occurred in the small airways, in which extensive mural inflammation and follicles caused obstruction. As the severity of bronchiectasis progressed there was loss of elastic tissue, muscle and cartilage. Interstitial pneumonia was present in all cases in the parenchyma adjacent to the affected bronchi.

Saccular bronchiectasis was uncommon and corresponded to cystic bronchiectasis. Atelectatic bronchiectasis generally involved a localised area of lung and appeared to arise from localised obstruction, often in the context of lymph node enlargement, as may occur with mycobacterial infection.
Pathophysiology

The dominant feature of bronchiectasis is airway inflammation in association with bacterial infection. It has generally been thought that the inflammation is secondary to non-clearing infection. There may be a disproportionate or exaggerated immune response to infection [13, 14], although this is hard to prove definitively.

The “vicious cycle hypothesis” was proposed by Cole [15] to explain the development of bronchiectasis. This model proposed that an initial event occurred, which compromised mucociliary clearance, allowing infection and colonisation of the respiratory tract. Bacteria caused inflammation, which damaged the respiratory tract, leading to more bacterial proliferation and more inflammation/damage. Thus an ongoing cycle developed which caused progressive destruction of the lung. The opinion of Cole [15] was that the primary event in this cycle was impairment of the mucociliary system; this mechanism is discussed in detail in the next section.

The current view is that a combination of a microbial insult and a defect in host defence allow establishment of persistent bronchial infection. The vicious cycle model is shown in figure 2.

Mucociliary system

The mucociliary system is part of the innate defence mechanism that clears unwanted material from the airways. It consists of the cilia, the periciliary fluid layer and the mucus layer. Mucus is normally cleared by successful interaction of the cilia with the mucus, and this depends on the beat frequency of the cilia, the mucus load and its physical properties, and the depth of the periciliary fluid layer. Abnormalities in any component of the mucociliary system can result in abnormal mucociliary clearance. The mucociliary system is demonstrated in figure 3.

In hypersecretory diseases, such as bronchiectasis, chronic inflammation in the airways results in an increase in the size and number of the mucus secretory cells, i.e. in hypertrophy of the submucosal glands, and in hyperplasia and metaplasia of the goblet cells extending to the bronchioles that are normally free of mucous secretory cells. Therefore, in bronchiectasis, there is excessive mucus secretion throughout the conducting airways, including the bronchioles, where mucus does not exist in the healthy state. The cilia cannot transport excessive loads of mucus. In addition, the cilia have been found to beat more slowly in bronchiectasis that is not related to genetic ciliary defects than in healthy subjects [16], a feature that could relate to inflammatory products, such as neutrophil elastase, or to bacterial products, especially in those colonised with Pseudomonas [17, 18]. Defects in the ultrastructure of cilia have been found in patients with bronchiectasis unrelated to immotile cilia syndrome, but these may not be of clinical importance [16, 19, 20].

Mucus in bronchiectasis can be highly viscoelastic and adhesive [21, 22]. These physical properties of mucus are greatly influenced by the hydration at the airway surface. When the secreted mucus volume is excessive, as in bronchiectasis, there is an imbalance between mucins and available water [23]. Dehydration of airway mucus in bronchiectasis is evident when the percentage of solids in sputum is greater than the normal 2–3% [22, 23]. The increase in the percentage of solids in the mucus of bronchiectasis patients, in addition to causing impairment to its transport, can potentially inhibit the motility of neutrophils within the mucus and, thus, their ability to kill bacteria [24]. When the solids were increased from 2.5% (a normal value) to 6.5%, neutrophils failed to kill bacteria [24]. Importantly, this evidence demonstrates the consequences of hypersecretion of mucus and the need for optimal hydration of mucus.

The increased production of mucus in bronchiectasis, together with the impairment of the mucociliary system, leads to accumulation of mucus, chronic cough, mucus plug formation, airway obstruction, bacterial colonisation and infections that fail to resolve completely. In bronchiectasis, the failure of the mucociliary system to transport mucus most likely relates to the abnormal load of mucus and the abnormal physical properties of the mucus, rather than to the cilia or their movement being abnormal, except in

Figure 2
Cycle of infection and inflammation. Based on the “vicious cycle hypothesis” described by Cox [15], a combination of a microbial insult and a defect in host defence allows the establishment of bronchial infection. This causes inflammation, which damages the respiratory tract, further, compromising host defence and resulting in increased burden of infection. This results in an ongoing cycle of infection and inflammation, causing progressive lung disease.
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Pathophysiology of bronchiectasis can also be considered in terms of the effect of bacteria on patients with genetic ciliary defects, such as primary ciliary dyskinesia (PCD). When the mucociliary system fails, cough becomes a very important mechanism for clearing mucus. Cough, however, can be also compromised in patients with bronchiectasis, because mucus is highly viscoelastic and sticky. Furthermore, for cough to be effective, a high expiratory flow is required and this is impossible for those patients with bronchiectasis who have severe air flow limitation [25].

The impairment of the mucociliary system and the abnormal properties of mucus in bronchiectasis have been well documented by many studies using a radioaerosol technique and imaging with a gamma camera [22, 26–31]. Whatever the cause of the bronchiectasis, the mucociliary system is greatly affected by the disease and, because of this, patients have common symptoms, such as chronic cough, sputum production and recurrent infections. The failure of the mucociliary system in bronchiectasis contributes greatly to the vicious cycle of the disease progression.

More recently, the scope of this cycle has been more broadly interpreted as including other forms of immune dysfunction in addition to the mucociliary apparatus. Currently, a commonly held view is that bronchiectasis occurs due to a combination of a defect in host immunity with persistent bronchial infection.

Specific effects of bacteria and pathogens

The pathophysiology of bronchiectasis can also be considered in terms of the effect of bacteria on the respiratory tract and the response of immune cells to these bacteria.

Bacteria have a number of effects on the respiratory tract, of which the best described is inhibition of mucociliary clearance [32]. *Haemophilus influenzae*, *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* produce mediators that inhibit ciliary function, damage ciliary epithelium and inhibit mucus transport. Bacteria may also destroy the epithelium, release chemotactic factors to attract large numbers of neutrophils [33, 34] and produce biofilms. Biofilms are best described in the context of *P. aeruginosa* infection [35], in which an impenetrable matrix is formed around the bacteria with severe damage to the underlying lung.

Neutrophils are found in large numbers in bronchiectasis [36–38]. One study found that following injection with radio-labelled white cells, 50% of the circulating neutrophils pass into the bronchi [39]. These neutrophils are most prevalent in the airway lumen and release mediators, such as protease and elastase, which destroy the bronchial wall elastin and epithelium. The bronchial cell wall is infiltrated predominantly by a mononuclear infiltrate of T-lymphocytes and macrophages, which appear to be the cells predominantly causing small airway obstruction [37, 40, 41].

**Lung function**

Patients with bronchiectasis generally have mild to moderate airflow obstruction. Both adults and children have been shown to develop progressively worsening airflow obstruction [42–44]. As bronchodilation is the key diagnostic feature, bronchiectasis is often not considered to be an obstructive lung disease. The explanation for this seeming paradox is that while the large airways are dilated the small airways are obstructed, and as most of the pulmonary tree is composed of small airways the net effect is obstruction. This effect has been best demonstrated in pathology studies such as those performed by Whitwell [12]. More recently, a computed tomography study has highlighted this mechanism [45]. This effect is demonstrated in figure 4.

Hogg et al. [46] have studied small airways obstruction in COPD and found the factor most associated with obstruction was the presence of lymphoid follicles, which were similar to those described by Whitwell [12] 50 years previously.

The volume of sputum [42], colonisation with *P. aeruginosa*, frequency of exacerbations and systemic inflammation [43] have been shown to be correlated with decline in lung function.
Airway reversibility may also be common in bronchiectasis. Murphy et al. [47] found significant airway reversibility in 40% of subjects and two other studies found a 30% [48] and 69% [49] prevalence of positive result to histamine challenge. Whether these findings indicate coexistent asthma has not been established. However, a recent study in a relatively large cohort of patients with bronchiectasis (n=95) showed that the prevalence of bronchoconstriction in response to inhaled mannitol was low: 19.4% in patients on inhaled corticosteroids and 27.1% in patients not on inhaled corticosteroids [50]. Allergic bronchopulmonary aspergillosis (ABPA) is a classical cause of bronchiectasis. However, studies of the inflammatory profile of bronchiectasis generally do not demonstrate the typical cells and mediators of atopy or asthma. It is possible that infection by itself may cause bronchoreactivity.

**Aetiology**

There are a large number of causes that have been proposed to cause bronchiectasis. As bronchiectasis is a heterogeneous condition with a long clinical history before the diagnosis is made, the exact role of potential causative factors is often not clear. It may be more appropriate to consider many of these causes as being risk factors (as occurs with risk factors in ischaemic heart disease) rather than the sole aetiological agent.

**Post-infectious bronchiectasis**

The most common cause of bronchiectasis described in the literature is childhood infection, particularly with pneumonia, whooping cough and measles [51–56]. This appears to be particularly important in indigenous populations with poor health and recurrent infection, such as Australian aborigines [6]. The mechanism of postinfectious bronchiectasis has not been well defined. To the authors’ knowledge, it has not been demonstrated in a study that one acute episode of infection results in immediate bronchiectasis. It may be that infection causes structural damage to the airways, allowing persistent infection that results in bronchiectasis. At some stage all patients become colonised with bacteria, but this appears to be a different entity from the descriptions in the literature of postinfectious bronchiectasis.

Several factors complicate the role of postinfectious disease [57]. The studies that describe this entity generally use long-term retrospective recall. The main causative infections are extremely common, with the seroprevalence of measles in unvaccinated populations more than 90% and whooping cough more than 50% [58].

Finally, patients with an immune deficiency are more likely to have significant lung infections.

Mucobacterial infections, both tuberculous and non-tuberculous, have a well recognised association with bronchiectasis. An important mechanism is probably lymph node obstruction and atelectatic disease, as described by Whitwell [12].

**Mucociliary defects**

It is important to distinguish between primary and secondary mucociliary defects in causing abnormal mucociliary clearance that result in bronchiectasis.

**Primary.** Bronchiectasis can develop as a result of abnormal mucociliary clearance caused primarily by a genetic ciliary defect, as in the PCD syndrome. This is a rare inherited condition in which the ciliary defect is the absence or shortening of the dynein arms that are necessary for the normal coordinated ciliary beat [59]. Approximately 50% of patients with PCD have Kartagener’s syndrome, characterised by bronchiectasis, sinusitis and situs inversus [59].

Another rare condition is Young’s syndrome, characterised by azoospermia and bronchiectasis that is primarily due to highly tenacious secretions that are poorly cleared. A degree of ciliary disorientation has been found in patients with Young’s syndrome but this may be due to the highly viscous and sticky secretions [60].

Measurement of the ciliary beat frequency and pattern and identification of the ultrastructural ciliary defects, together with the family history and presence of infertility can help to...
diagnose the cause of mucociliary dysfunction resulting in bronchiectasis.

**Secondary.** Abnormal loads of mucus can slow down ciliary beat frequency. In addition, slowing of the ciliary beat can be caused by inflammatory products, such as neutrophil elastase, or by bacterial products, especially in those colonised with *Pseudomonas* [17, 18]. Defects in the ultrastructure of cilia have been found in patients with bronchiectasis unrelated to immotile cilia syndrome, but these may not be of clinical importance [16, 19, 20].

Mucus, once secreted, can become highly viscoelastic and adhesive as a result of imbalance between the mucins and water available at the airway lumen, as described previously. These secondary problems develop after the initial infection early on in the disease and certainly contribute to the progression of the disease.

**Obstruction.**
Mechanical obstruction is an important cause of bronchiectasis and will generally result in localised disease. It is important to diagnose obstructive disease early, as removal of the obstruction has great benefit. Causes of obstruction include an inhaled foreign body, slow-growing tumour and twisting of an airway after lobar resection. Retained sputum can contribute to obstruction as well and Cole [57] felt that this had an important role in bronchiectasis.

**Immune dysfunction.**
A key factor in the pathogenesis of bronchiectasis is failure of the immune response to clear infection, and this has a number of causes, including mucociliary disorders and obstruction.

In this review we use the term immune dysfunction to describe a specific disorder associated with abnormal immunity. There are an increasing number of conditions associated with bronchiectasis, including HIV, hypogammaglobulinaemia, type 1 major histocompatibility complex deficiency and TAP1 deficiency [2]. The role of immunoglobulin subclass deficiency is controversial.

ABPA is a classical cause of bronchiectasis and is usually manifest by central disease. Bronchiolitis obliterans that occurs in lung transplantation may have bronchiectasis in its late stage [61].

Perhaps the most common factor associated with immune dysfunction is malnutrition or socioeconomic disadvantage. As described in the epidemiology section, bronchiectasis is a major problem in indigenous populations and also probably in developing countries. Therefore, malnutrition and socioeconomic factors may have a role in precipitating immune dysfunction and be a risk factor for bronchiectasis.

**Extremes of age.**
There is a higher incidence of infection in early childhood and old age, as the immune system is less effective [62, 63]. Studies of bronchiectasis have generally described the onset of a chronic productive cough and respiratory symptoms in the first 5 years of life. Field [64] performed a long term prospective study on a cohort of children with bronchiectasis, and found these subjects generally improved regardless of treatment when they reached adolescence. In our patients with childhood disease we have found that these subjects improved as adolescents and then became worse in their 50s and 60s, when they tended to re-present for medical review [42, 65].

We have also described a cohort of healthy adults with no previous symptoms or risk factors for respiratory disease who developed persistent productive cough over the age of 50 years and were found to have bronchiectasis [66]. Weinberger et al. [8] reported a prevalence of bronchiectasis as being 4.2 per 100,000 population aged 18-34 years and 272 per 100,000 in those aged over 75 years [8].

**Chronic obstructive pulmonary disease.**
Two recent studies have described a high prevalence (29% and 50%) of bronchiectasis in cohorts of patients with COPD [9, 10]. Patel et al. [10] found that the presence of co-existent bronchiectasis was associated with worse airway inflammation and exacerbations. These studies suggest that the chronic bronchitis that is a defining feature of COPD may frequently cause bronchiectasis.

There is also considerable overlap in the pathology of the two conditions in that: 1) the predominant inflammatory cells are the neutrophil, macrophage and T-lymphocytes; 2) proteases and elastases cause pulmonary damage; and 3) lymphoid follicles are associated with airflow obstruction.

**Other causes.**
Rheumatoid arthritis is strongly associated with bronchiectasis. The prevalence of associated bronchiectasis on HRCT is up to 30% [67, 68]. Bronchiectasis may occur in other inflammatory conditions, such as Sjögren’s syndrome [69], Churg-Strauss syndrome [70] and inflammatory bowel disease [71].

α1-Antitrypsin (AAT) deficiency is strongly associated with airway diseases, including COPD and bronchiectasis. Parr et al. [72] found, in a cohort of 74 subjects with AAT deficiency, that
70 subjects had evidence of radiological bronchiectasis and 20 had the syndrome of clinical bronchiectasis (with productive cough, etc.). Recurrent aspiration may be associated with bronchiectasis, although its role is still not well defined. Aspiration of chemicals or heroin overdose may cause bronchiectasis. One study reported that infection with Helicobacter pylori was significantly associated with bronchiectasis, while another study found no such association [2].

Microbiology
The microbiology of bronchiectasis is complex, with multiple potential pathogens. The pattern of isolates varies between different institutions. Previous studies have shown that the two major pathogens found are H. influenzae, which is nearly always nontypeable, and P. aeruginosa. Other important pathogens include Moraxella catarrhalis, S. pneumoniae, non-tuberculous mycobacteria and Aspergillus species. A consistent finding is that, despite the presence of purulent sputum, 30–40% of specimens will fail to grow any pathogens (even using bronchoscopy and protected brush) [73–76].

The bronchi demonstrate a significant turnover of pathogens and this has been best demonstrated with Moraxella (formerly Branhamella), in which a new strain was acquired every 2 months [77].

As bronchiectasis progresses there appears to be a change in bacterial flora [76]. Subjects with the mildest disease usually have no pathogens isolated; while subjects with moderate disease most commonly have H. influenzae. In subjects with the most severe disease, P. aeruginosa is the dominant pathogen. Biofilm-producing P. aeruginosa is reported by microbiology laboratories as being mucoid in phenotype and may be untreatable.

Diagnosis
The diagnosis of bronchiectasis is made when patients have the clinical syndrome of bronchiectasis and specific radiological features on HRCT scanning.

Clinical features
The clinical syndrome can be considered to be a form of severe bronchitis. Virtually all subjects will have a cough productive of purulent sputum, most commonly every day. Other important symptoms include dyspnoea, haemoptysis and fatigue. Most subjects will have at least one exacerbation per year. Upper airway involvement with rhinosinusitis is a prominent feature, particularly in those with childhood onset disease. The main feature on examination is the presence of crackles, which are most commonly found in the bilateral lower zones [65].

Radiology
Plain chest radiography is relatively insensitive for diagnosing bronchiectasis, and will usually only show interstitial markings. Computed tomography scanning with high resolution should be used to diagnose bronchiectasis as this technique demonstrates the Airways in higher detail than standard computed tomography scanning. NADICH et al. [78] and MCCUNNIS et al. [79] have established the use of standard criteria for the diagnosis of bronchiectasis. The most specific features are: 1) internal diameter of a bronchus is wider than its adjacent pulmonary artery, 2) failure of the bronchi to taper, and 3) visualisation of the bronchi in the outer 1–2 cm of the lung fields. Less specific features include mucosal wall thickening, crowding of the bronchi and mucus impaction. Mucosal wall thickening is associated with inflammation and increased decline in lung function [80].

The lobes most commonly involved in bronchiectasis are the lower lobes and usually multiple lobes are involved. Localised disease may suggest obstruction. A mosaic pattern on expiration is consistent with small airway bronchiolitis.

Other tests
At the time of diagnosis, other tests looking for aetiological factors, sputum analysis and lung function should be performed. These will be discussed in more detail in the accompanying article on the management of bronchiectasis [81].

Syndrome of chronic suppressive lung disease and chronic bronchitis CHANG et al. [82] have used the term chronic suppressive lung disease to describe children who have the clinical entity of bronchiectasis but are not able to undergo HRCT. The opinion is that these subjects should be considered to have a diagnosis of bronchiectasis and should be managed as such.

Many adults have severe bronchitis with purulent sputum production but a HRCT scan which is negative for bronchiectasis. The suspicion is that many of these subjects will go on to develop radiological bronchiectasis but this has not been proven. Such subjects may benefit from a bronchiectasis management plan, but this also has not been assessed in any clinical trials.

Finally, some subjects have a computed tomography scan that demonstrates bronchiectasis but have no clinical features of bronchitis. Patients in this category can probably just be observed.

Educational questions
1. What is the most common finding on physical examination?
   a) Clubbing
   b) Wheeze
   c) Cyanosis
   d) Basal crackles
   e) Upper zone crackles
2. What bacterium is most commonly found in severe disease?
   a) Streptococcus pneumoniae
   b) Pseudomonas aerea
   c) Staphylococcus aureus
   d) Haemophilus influenzae
   e) No growth
3. What are the predominant inflammatory cells present in the bronchial wall?
   a) Lymphocytes and macrophages
   b) Neutrophils and macrophages
   c) Eosinophils
   d) Mast cells
   e) Neutrophils
4. Excessive mucus production and impaired mucociliary clearance lead to:
   a) Mucus accumulation
   b) Airway obstruction
   c) Bacterial colonisation
   d) Recurrent infections that fail to resolve
   e) All of the above
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