Bronchiectasis

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Abstract

Bronchiectasis is clinically defined as irreversible airways dilatation associated with chronic inflammation and infection. It is a cause of chronic cough and recurrent lower respiratory tract infections. The prevalence of diagnosed bronchiectasis is probably increasing as a result of an ageing population and the increased use of radiological investigations. The diagnosis is secured by high-resolution computed tomography of the chest, which should prompt referral to a specialist unit to investigate for one of many underlying causes. These can be diagnosed in up to 65% of patients and when made can significantly alter management. The pathogenesis of bronchiectasis is best understood as a vicious cycle of inflammation and infection. Although clinical trial data are often lacking, there are many treatment options that target each of the steps within this cycle. These include the use of airway clearance techniques, mucoactive agents, anti-inflammatories and antibiotics for both exacerbation and prophylaxis. This intensive approach is necessary as there is a considerable associated morbidity, mortality and health economic cost. However, patient adherence to such complex and long-term treatment can be difficult. This article discusses the epidemiology, pathogenesis, diagnosis and management of bronchiectasis.

Keywords Antibiotic strategies; bronchiectasis; bronchiectasis severity index; nebulized antibiotics; specific antibodies; vaccine response

Key points

- Bronchiectasis is the common structural endpoint of a number of diseases
- The Bronchiectasis Severity Index, a clinical scoring system that quantifies the risk of hospitalization and mortality, has recently been defined and validated
- Treatments are targeted at each step of the pathogenesis of this disorder
- There is now more clarity from recent clinical trials on the choice of nebulized antibiotic prophylaxis
- Novel immunodeficiencies causing bronchiectasis, such as the activated PI3K-delta syndrome, continue to be reported

Definition

Bronchiectasis is a pathological term used to describe irreversible airways dilatation often accompanied by the formation of a chronic inflammatory exudate. It was first described by Laennec in the 19th century and is the structural endpoint of a number of diseases. Clinically, it leads to a chronic productive cough, obstructive airways disease and recurrent chest infections.

Epidemiology

It has proven challenging to accurately estimate the incidence and prevalence of bronchiectasis. As the common structural endpoint of a number of disease processes, it is often not reported separately from the more severe or primary pathology. For example, one study found that as many as 50% of patients with a diagnosis of chronic obstructive pulmonary disease had computed tomography (CT) evidence of bronchiectasis. There have been multiple epidemiological reports with wide-ranging estimates of incidence, and consensus has been confounded by variance in disease definition as well as other factors.

There is also a hypothesis that, at least in more developed countries, the incidence of bronchiectasis has been decreasing perhaps as a consequence of the widespread use of antibiotics and the implementation of childhood vaccination programmes. For example, a study conducted in 1953 in Bedford, UK, reported an incidence of 1.3 per 1000 people, whereas more recent studies have shown much lower rates, such as 2.7 per 100,000 people in Finland and 3.7 per 100,000 children in New Zealand. This reduction has not, however, been seen in all countries and across all ethnicities. The same New Zealand study identified an incidence of 1.5 per 100,000/year in children of European origin compared with 4.8 in Maoris and 17.8 for Pacific Island children. Furthermore, and in keeping with the chronic progressive nature of the disease, a US study identified a prevalence of 17.8 per 100,000 in 18–34 year-olds rising to 271.8 per 100,000 in individuals >75 years. These data suggest that we are likely to see an increasing prevalence in the developed world as a consequence of an ageing population and increased use of diagnostic imaging.

There have been a number of reports of early onset bronchiectasis in HIV-infected children. A retrospective case-controlled study of HIV-infected children in the US followed up in a single institution between 1982 and 2000 identified that 5.7% developed bronchiectasis at a mean age of 7.8 years. All the children with bronchiectasis had low CD4 counts consistent with a Centers for Disease Control immunologic classification 3, but viral load was not assessed. Recurrent pneumonia and lymphocytic interstitial pneumonitis were also identified as risk factors. These data should clearly be interpreted in light of advances in the treatment of HIV infection. However, a more recent study has highlighted the continuing challenge of morbidity associated with bronchiectasis in HIV-infected children despite highly active antiretroviral therapy.

Finally, there is a considerable morbidity and health economic burden associated with bronchiectasis. A recent multicentre European study identified an exacerbation rate of 1.8–3 per year, with up to 31% of patients requiring hospitalization over a 2-year period.[1] Furthermore, a Belgian study of 245 patients with bronchiectasis found that overall mortality was 20.4% over a

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median follow-up of 5 years, 58% of these deaths being related to respiratory disease.

Pathology

The histopathological appearances of bronchiectasis are of dilated airways larger than the accompanying pulmonary artery and filled with an inflammatory exudate dominated by macrophages and neutrophils. The underlying respiratory epithelium is altered to a squamous metaplasia, sometimes with ulceration, and lacks ciliated cells, which impedes mucus clearance. The bronchial wall is weakened as a consequence of a loss of elastin and smooth muscle. There is often bronchial wall thickening caused by peribronchial fibrosis and a chronic inflammatory cell infiltrate accompanied by the formation of germinal centres. Eosinophils or granulomas may be present, either as a reflection of chronic inflammation or in association with fungal or mycobacterial infection. There is often obliteration of small airways, which contributes to the airflow obstruction. As a consequence of the cycle of inflammatory destruction followed by healing, there is formation of bronchopulmonary anastomoses and enlargement of bronchial arteries, which can lead to airway haemorrhage and haemoptysis.[2]

There has been significant progress in recent years in our understanding of the molecular and cellular pathogenesis of bronchiectasis. There appear to be defects in lung defence mechanisms (mechanical, humoral, cellular), and there is now good evidence to support a pathological role for chronically infecting bacteria.

Mechanical

Reductions in the cough reflex are associated with recurrent chest infections, and recurrent aspiration is certainly a well-recognized cause of bronchiectasis.

The mucociliary escalator functions to move inhaled organic and inorganic particles caught in mucus to the throat. This viscous layer is propelled by cilia that beat in a coordinated fashion within a more fluid and tightly regulated airways surface liquid (ASL). Changes in the electrolyte composition of the ASL, as seen in cystic fibrosis (CF), lead to an altered volume and height of this more fluid layer and so impair ciliary movement. Genetic defects in the structure of the proteins making up the cilia also lead to abnormal movement and are the cause of primary ciliary dyskinesia. Finally, airway infection itself, whether viral or bacterial, can directly impair cilial function.

Immunity

Both the adaptive and innate immune systems contribute to humoral and cellular mechanisms of defence in the lung.[2] It is beyond the scope of this article to describe these in detail, but there is a complex and multilayered response to infection involving multiple receptors and cell types. Defects in many of these pathways have been described in patients with bronchiectasis. For example, abnormal antibody production, seen in patients with common variable immunodeficiency (CVID), is central to pathogenesis and is treatable with immunoglobulin (Ig) replacement.

Our understanding is evolving, and new molecular defects to explain clinical syndromes continue to be described. A recent genetic study identified a dominant gain-of-function mutation in the *PIK3CD* gene, which encodes a catalytic subunit of phosphoinositide 3-kinase delta (PI3K-delta). This activated PI3K-delta syndrome (APDS) is characterized by recurrent respiratory infections, progressive airway damage, lymphopenia, increased circulating transitional B cells, increased IgM and reduced IgG2 concentrations and impaired vaccine responses.[3]

Chronic infection

There is evidence to support a role for chronic infection in the progression of bronchiectasis. Studies using conventional sputum culture techniques have shown that bacteria can be cultured from 65 to 79% of chronically productive patients even when they are clinically stable. The most common pathogens are *Haemophilus influenzae* and *Pseudomonas aeruginosa*.[2] More recent studies using sequencing of bacterial 16S ribosomal DNA have shown that pathogenic bacteria can be detected in all sputum samples from bronchiectatic patients. Bacterial colonization has been associated with clinically important outcomes such as frequency of pulmonary exacerbation and hospitalization. Finally, *P. aeruginosa* is associated with a particularly difficult clinical course characterized by a more rapid loss of lung function, frequent exacerbations and increased mortality.

A vicious cycle of infection and inflammation

Clinically, the most helpful unifying concept of the pathogenesis of bronchiectasis remains Cole's vicious cycle of inflammation and infection. This describes a primary insult causing bronchial wall inflammation followed by disordered mucociliary clearance, chronic or recurrent infection, bronchial wall damage, airflow obstruction and further inflammation that perpetuates the cycle (Figure 1).

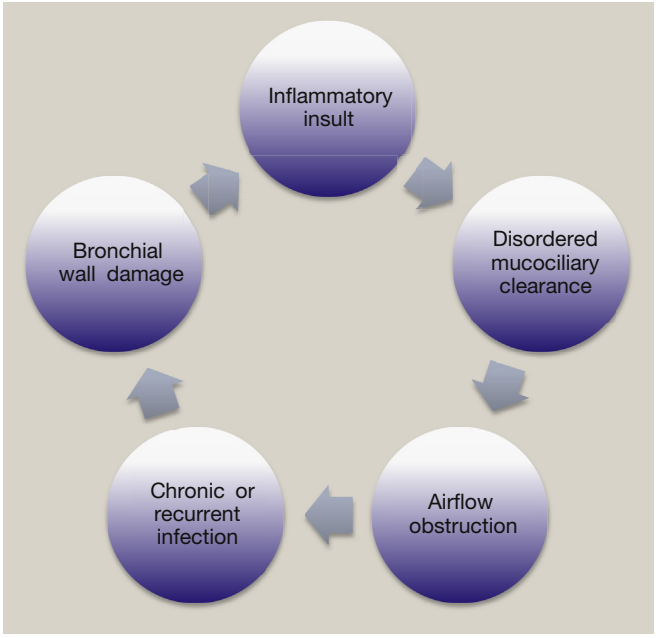

Figure 1 Cole's hypothesis of a vicious cycle of infection and inflammation.