

Introduction



Key points

- Patients with bronchiectasis typically have chronic airway infection, punctuated by acute exacerbations and accompanied by progressive airflow obstruction.
- Bronchiectasis occurs in cystic fibrosis (CF), primary ciliary dyskinesia and primary immunodeficiencies and is also associated with systemic diseases, including inflammatory bowel disease and rheumatoid arthritis.
- Computed tomography is often necessary for confident diagnosis of bronchiectasis.
- Management of non-CF bronchiectasis is largely based on evidence extrapolated from studies in CF and COPD.

Bronchiectasis means dilatation of the airways; this occurs patchily due to scarring and is usually associated with mucosal thickening, mucus plugging and a variable degree of lung over-inflation. Bronchiectasis is associated with a range of common and rare diseases, some of which impact on mucociliary clearance and immunity. Mucus clearance and local defence mechanisms against microorganisms are critically important in keeping the lungs free of infection. When they are impaired, repeated infection causes damage which further impedes the clearance of mucus. The airway dilatation and consequent impairment of mucociliary clearance combine to further increase susceptibility to repeated infection in the lungs, resulting in chronic infection in some cases. The abnormal airway anatomy, chronic infection and mucus retention result in a slow decline in respiratory function. In the early stages of the disease, even with significant evidence of bronchiectasis on computed tomography (CT), spirometry may be normal; in advanced disease, functional evidence of airway obstruction is usual. The apparent paradox of the structural bronchodilatation of airways but functional evidence of diffuse narrowing, largely reflects the different generations of airways involved; there may be irregular bronchodilatation of medium-sized airways but airflow is determined more by the smaller airways, which are narrowed due to chronic inflammation and scarring.

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As a diagnostic term, bronchiectasis is sometimes prefixed by non-cystic fibrosis (non-CF) to exclude this specific cause from that associated with another condition or in which no cause is identified. Bronchiectasis is, however, primarily a pathological description of the airways; although an aetiological diagnosis can only be established in some patients with definite CT radiological evidence of the condition, bronchiectasis is a useful diagnostic term as patients share a common symptomatology.

Epidemiology



The prevalence and incidence of bronchiectasis are not known accurately. Prevalence has been estimated to be from 0.013 cases per 100 000 population in 1954 in the UK and 0.5 per 100 000 in Finland in 1998, to 4 per 100 000 in people aged 18–34 years, rising to 272 per 100 000 in over those over 75 years of age in the USA in 2005. In New Zealand, the reported prevalence is 3.7 per 100 000 population but this varies according to ethnicity. Bronchiectasis is particularly common in children of Pacific Island descent compared with European children. In a sample of 5% of Medicare data in the USA, the 8-year period prevalence of bronchiectasis was 1106 cases per 100 000 population, and in this study the prevalence of bronchiectasis increased by about 8.7% per year of life. This report also suggested a higher prevalence in Asian- compared to African- and European-Americans.

In Europe, age-standardised hospital admission rates vary from less than 2 to more than 6 per 100 000 population (figure 1). This is lower than the estimated average annual age-adjusted hospitalisation rate in a US study, which found 16.5 hospitalisations per 100 000 population and an increase of 2.4% among men and 3.0% among women between 1993 and 2006. In the US study, women and people aged > 80 years had the highest rate of bronchiectasis-associated hospitalisations. The differences between the USA and Europe perhaps reflect the quality of available data.

Prognosis in people with bronchiectasis is not clear, but it is definitely related to lung function and the presence of infection, particularly *Pseudomonas aeruginosa*. A study from the UK suggests that the number of deaths due to bronchiectasis is increasing at 3% per year.

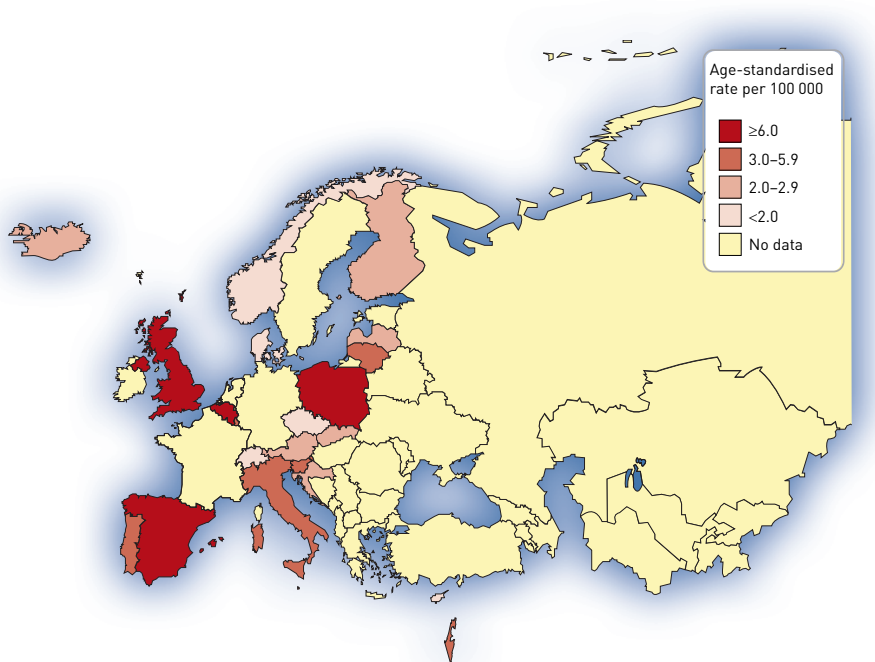


Figure 1 – Hospital admission rate for bronchiectasis. Data from the World Health Organization Hospital Morbidity Database, October 2011 update, and Eurostat, March 2012 update. Data are not shown for the following countries where bronchiectasis is reported in combination with chronic obstructive pulmonary disease: Germany, France, Hungary, Ireland, Macedonia, the Netherlands, Romania, Sweden and Turkey.

Causes/pathogenesis



The way in which bronchiectasis develops in the airways is poorly understood. The primary cause is not known in conditions other than CF, primary ciliary dyskinesia (PCD) syndromes and primary immunodeficiency syndromes. In CF, impairment of mucociliary clearance is the result of abnormal airway hydration due to CF transmembrane regulator (CFTR) mutations. In PCD it is due to abnormal structure and function of cilia. In other groups of patients with bronchiectasis, it is assumed that infection and/or perturbed innate or acquired immunity are important factors, with secondary impairment of mucociliary clearance.

In established disease, there is a vicious cycle of inflammation driven by neutrophils, recurrent or persistent infection, primarily with *Haemophilus influenzae* and injury to epithelium and bronchial and bronchiolar structures (figure 2). The anatomical damage further impairs mucociliary clearance; inflammation through proteases impairs some important aspects of innate immunity in the airways, causing further persistence of this vicious cycle. While this process is widely accepted as a paradigm for the condition, there are a number of key parts of the pathway which are poorly understood.

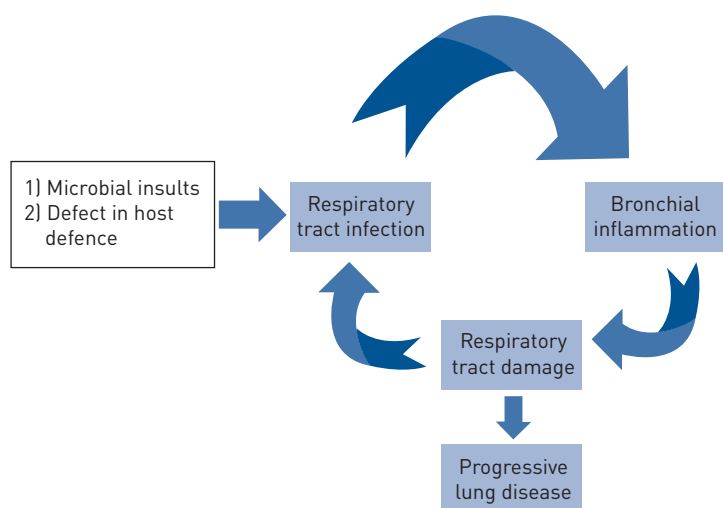


Figure 2 – The vicious cycle of infection and inflammation leading to progressive lung disease in bronchiectasis.

In people with bronchiectasis, a diagnosis of an underlying associated condition can be made in about 50% of cases. Many studies of diagnosis begin by excluding people with CF, and in some diagnostic and treatment guidelines the condition is labelled as non-CF bronchiectasis, to capture all of the other conditions. However, there is no intrinsic pathological difference between bronchiectasis associated with CF and bronchiectasis due to other conditions. In general, in CF, lung disease is more aggressive and associated with a higher prevalence of Gram-negative infection, particularly with *P. aeruginosa*. Bronchiectasis is almost universal in people with CF (see chapter 14). It is also a common complication of PCD and primary immune deficiency disorders, particularly common variable and X-linked immunodeficiency associated with reduced blood concentrations of immunoglobulin (Ig)G. Bronchiectasis also occurs, uncommonly but with increased frequency, in a number of systemic immune conditions, particularly rheumatoid arthritis and inflammatory bowel disease. Bronchiectasis is associated with infection due to HIV, non-tuberculous mycobacteria and *Mycobacterium tuberculosis*. The pathophysiological connection between these conditions and bronchiectasis is poorly understood. However, in many patients with a diagnosis of bronchiectasis, there is no clear association with another underlying disease. Childhood infections, such as whooping cough (pertussis) and measles, have been considered as strongly associated or causative. However, problems with recall bias make it very difficult to know the importance of this association.

Bronchiectasis may also complicate a range of other lung diseases: it can be identified in some patients with chronic obstructive pulmonary disease (COPD), severe asthma and interstitial lung disease. In these conditions, bronchiectasis is usually found in the context of severe disease and is then not considered the primary disease. However, when it occurs alongside these conditions, it is associated with a higher incidence of infective pulmonary exacerbations and some of the management strategies used for primary bronchiectasis may be effective.

Clinical manifestations and consequences



Bronchiectasis causes cough, usually productive of sputum. This may occur daily or less frequently in patients with early disease. These regular symptoms are punctuated

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by episodes of pulmonary exacerbation, often associated with culture of a potentially pathogenic organism in sputum. It is generally unclear whether these are new infections or a resurgence of chronic infection. It may be that both are important precipitants. The exact cause of pulmonary exacerbations is not well understood; however, these episodes are associated with a change in sputum colour towards green, along with an increase in cough frequency and sputum volume. This is sometimes complicated by minor haemoptysis. Individuals may feel more breathless and some will have systemic symptoms of infection, such as fever, fatigue and general malaise. Pulmonary exacerbations are associated with disease severity, and though there is no direct data for bronchiectasis, exacerbations are likely to contribute to a decline in lung function.

Chest crackles are heard on clinical examination, though in mild disease there may be no abnormal clinical signs. Finger clubbing is classically associated with bronchiectasis, but it is now a rare manifestation in this condition. Forced expiratory volume in 1 second (FEV1) is frequently used for clinical monitoring to assess the severity of functional abnormality. In general, however, FEV1 changes little during exacerbations and its value as an outcome measure in clinical trials and in clinical monitoring has been questioned. As disease progresses, there is a continuing reduction in spirometric volumes. In some patients, over-inflation of the lungs is prominent and this has been associated with higher mortality.

High-resolution CT is the diagnostic modality that defines bronchiectasis. Plain chest radiography is insufficiently sensitive for diagnostic purposes. There are a number of scoring schemes for reporting severity using CT, which are rarely used in clinical practice but are important for clinical research purposes. Other diagnostic tests should seek to systematically identify underlying causes such as CF, PCD, impaired immune function, allergic bronchopulmonary aspergillosis and α_1 -antitrypsin deficiency.

Prevention



It has been suggested that the widespread application of vaccination programmes in childhood, particularly against measles and pertussis, should cause a significant reduction in the prevalence of bronchiectasis. However, there are no data to support this association. In a recent systematic review of the long-term consequences of childhood pneumonia, bronchiectasis was uncommon, and asthma and COPD were more common. In addition to universal childhood vaccination,

it would be prudent to recommend careful treatment of episodes of childhood pneumonia and immunisation against influenza and pneumococcus in appropriate individuals of any age.

Many patients with bronchiectasis have a significant delay in diagnosis and may be labelled as simply having lower respiratory tract infections or an alternate respiratory diagnosis of COPD or asthma. In these cases it is not clear whether earlier specific diagnosis would improve outcomes, but the diagnosis should be considered in all patients presenting with persistent cough productive of sputum. In CF, there is good evidence that the natural history of bronchiectasis can be positively affected by effective antibiotic therapy and drugs that improve mucociliary clearance (see chapter 14). Such evidence is not available in non-CF bronchiectasis.

Management



The principles of management of bronchiectasis are outlined in table 1. There is a great lack of clinical trials in bronchiectasis to guide treatment. These therapeutic choices have been extrapolated from COPD or CF treatment regimes, with variable levels of success. Some small investigator-led randomised controlled trials have been published, but there are insufficient data to recommend definitive therapies based on robust clinical trials. Regular airway clearance is a logical treatment and is supported by some small studies. Airway clearance, undertaken once or twice daily using methods such as the active cycle of breathing technique or a resistance device such as Acapella (Smiths Medical) or Flutter (Axcan Scandipharm Inc.), is a reasonable regimen. Inhaled β_2 -agonists may be helpful in managing associated airflow obstruction. There is some evidence to support the use of inhaled corticosteroids to reduce sputum volume and possibly the frequency of exacerbations in patients with *P. aeruginosa* infection. There are strong published data supporting the use of macrolides in CF and oral macrolides may also be of value in reducing exacerbations in non-CF bronchiectasis. Three randomised placebo-controlled trials of macrolide treatment have demonstrated a reduction in pulmonary exacerbations and an improvement in lung function (FEV1). This treatment should be considered in all patients with bronchiectasis who have had two or more exacerbations in the previous year. The use of inhaled antibiotics has been extrapolated from CF data. In individuals in whom chronic *P. aeruginosa* infection is identified, long-term antibiotics are often used. There are no therapies licensed for use in this condition, but off-label colistin, gentamicin and tobramycin are frequently used. In patients with newly isolated *P. aeruginosa*, eradication regimes are frequently applied based on experience from CF.

Treatment of pulmonary exacerbations should include increased airway clearance and the commencement of antibiotics. Choice of antibiotic is largely empirical, though previous sputum bacteriology results can be useful in deciding. For the common organisms, such as *H. influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus* and *Streptococcus pneumoniae*, oral antibiotics are usually sufficient. In contrast, for patients chronically infected with *P. aeruginosa*, combination therapy with an extended-action β -lactam and aminoglycoside is recommended. Surgery has a limited role in the management of bronchiectasis, mainly in localised disease. Occasionally, haemoptysis is sufficiently frequent or severe to warrant treatment by embolisation of the relevant bronchial artery or arteries.

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A diagnosis
of an
underlying
associated
condition can
be made in
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cases
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Improving airway clearance	Mechanical airway clearance (ACBT, PEP devices, autogenic drainage) Inhaled hypertonic saline Inhaled mannitol#
Reducing bronchoconstriction	Short- and long-acting β_2 -agonists
Reducing inflammation	Inhaled corticosteroids Oral azithromycin#
Treating infection	Oral antibiotics for exacerbations Inhaled colistin/aminoglycoside for eradication or long-term suppression

Table 1 – Therapies for bronchiectasis. (Many of these therapies are used but none are approved by European Medicines Agency to support their long-term use in bronchiectasis.) ACBT: active cycle of breathing technique; PEP: positive expiratory pressure. #: recently reported phase 3 clinical trials.

Prognosis



The prognosis of bronchiectasis is undefined. One UK study has shown evidence of some increase in bronchiectasis as a certified cause of death. A number of factors contribute to poorer outcome, such as low FEV1 and *Pseudomonas* infection.

Future developments



Bronchiectasis is one of the most neglected diseases in respiratory medicine. Currently there is no clear definition or classification of the condition and very little is known about its true prevalence or its impact on length and quality of life. There are no specifically licensed therapies and few specialist clinical services. Significant research is needed in order to improve the quality of care of patients with this condition.

Research needs



There are clear research needs in order to develop an evidence base for understanding the pathophysiology of bronchiectasis. In clinical research, there is an urgent need to determine the optimal long-term therapies that maintain lung function and quality of life, and reduce exacerbations. The optimal treatment interventions for exacerbations also require further study.



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