Chapter 1

Bronchiectasis: epidemiology and causes

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Summary

Bronchiectasis remains a significant cause of morbidity and mortality in the developed world. The true prevalence of the condition remains elusive, in part, because of the innate difficulty in determining causation, when more than one respiratory condition exists in the same patient, but also due to the increasing rate of diagnosis by radiological means where no clinical symptoms are present. The wide ranging aetiology of bronchiectasis will be discussed in this chapter; however, some aspects will be discussed in greater detail throughout this Monograph.

The diagnosis of bronchiectasis should be the beginning of a targeted search for causation, which may lead to directed treatment, thereby limiting the disease progression. Over the next 5 years a reduction in the number of cases labelled as idiopathic bronchiectasis should be expected, as the continual expanding knowledge of immunology and immunogenetics, with respect to large studies of patients with bronchiectasis, can be applied.

Keywords: Aetiology, bronchiectasis, epidemiology, non-cystic fibrosis

Bronchiectasis was first described by Laennec [1] in 1819 as part of a wider work describing the use of his novel invention, the stethoscope. In his book “De l’Auscultation Mediate ou Traite du Diagnostic des Maladies des Poumons et du Coeur” [1], he described the condition through the use of case reports, detailing clinical examination and correlating this with post mortem findings. He identified that any illness characterised by chronic sputum production could lead to bronchiectasis with tuberculosis and pertussis infection identified as the most likely causative conditions.

A century later, in 1919, A. Jex-Blake delivered a lecture at the Hospital for Consumption (London, UK) on the condition of bronchiectasis [2]. He examined the case records for the hospital over a 20-year period and gave a detailed account of the condition and its causes. He identified that bronchiectasis itself was a secondary condition to a preceding disorder of the lung and,
as such, its frequency was likely to be underestimated as the preceding condition was of such severity that the presence of bronchiectasis was overlooked. He also identified that the condition was apparent in 2% of the hospital’s admissions over the same 20-year period, but estimated that the true figure could be as high as 5%. Perhaps, unsurprisingly, in this pre-antibiotic era a third of patients were identified as having bronchiectasis secondary to an episode of pneumonia or pleurisy, a third due to chronic bronchitis and a further third due to bronchial obstruction, the majority of which were malignant tumours.

Since the introduction of antibiotic therapy the incidence of bronchiectasis due to tuberculosis or other infections decreased markedly from the beginning of the 20th century. Perhaps the most striking evidence for the effect of antibiotic introduction was a report in 1969 by Field [3] into childhood admissions for the condition. The author reported a reduction from 24–99 per 10,000 hospital admissions to 6–13 per 10,000 admissions for five large children’s hospitals between 1952 and 1960.

Despite this decline in cases in the antibiotic era of medicine, non-cystic fibrosis (CF) bronchiectasis remains a significant cause of morbidity.

### Epidemiology

Remarkably the current knowledge of the true incidence of bronchiectasis has changed very little from when A. Jex-Blake gave his lecture almost a century ago. In part, the reason for this remains similar to what was perceived in 1919. Bronchiectasis is often noted as a secondary phenomenon to a more severe pulmonary pathology, as is the case of asthma or chronic obstructive pulmonary disease (COPD), and as such goes unreported. Conversely, the widespread use of computer tomography (CT) as a diagnostic tool in respiratory medicine has resulted in the identification of an increased number of radiological bronchiectasis cases in patients who showed no symptoms and who would have otherwise not been classified as having it. Future studies of the prevalence of bronchiectasis should not be confined to radiological evidence alone but should include the assessment of clinical symptoms.

One of the first large-scale studies to determine the incidence of bronchiectasis was performed in 1953 and examined the population of Bedford, a town in the UK [4]. The authors identified an incidence of bronchiectasis as 1.3 per 1,000 people. The relevance of this data, collected prior to the widespread use of antibiotics and where the authors excluded patients with bronchiectasis as a consequence of other pulmonary pathology, is perhaps limiting. However, more recent data has been collected from cohorts in Finland, New Zealand and the USA [5–7]. The data from Finland suggested an incidence of 2.7 per 100,000 people, while in New Zealand an overall incidence in children of 3.7 per 100,000 was noted but showed wide variations with regards ethnicity. For example, children from a Pacific Island descent had an incidence of 17.8 per 100,000 compared with an incident of 1.5 per 100,000 for those of a Northern European descent.

Unsurprisingly, given the often chronic nature of its development, the prevalence of bronchiectasis and hospital admission related to bronchiectasis increased with age. Studies from the USA estimate a prevalence of 4.2 per 100,000 people in those aged 18–34 years, increasing to 271.8 per 100,000 in people aged >75 years [7].

### Aetiology

There are a wide range of conditions that can cause bronchiectasis and there are a number of ways in which one could classify these aetiological factors; however, an approach based on pathological processes appears to be the most logical and is described in table 1.

Bronchial dilatation can be caused by a structural defect in the wall itself, an effect of abnormal airway pressure on the bronchial wall or by damage to the airway elastic tissue and cartilage as a result of bronchial wall inflammation.
Inflammation within the bronchial wall can be the result of an infection within the airway, inhalation of injurious agents or an endogenous condition such as an autoimmune disease.

The lungs are continuously exposed to inhaled pathogens and have developed an advanced mechanism for trapping and removing them. The human airways are lined with ciliated epithelium with submucosal goblet cells secreting mucus that makes up the top layer of the airway surface liquid, the lower layer being the periciliary fluid that bathes the cilia and ensures they function appropriately. In healthy individuals the mucus traps inhaled pathogens and the continuously motile cilia transport the mucus and its contents out of the lung. Any defect in this mucociliary clearance mechanism can lead to the retention of pathogens resulting in the progression of airway infection, inflammation and ultimately bronchiectasis.

### Structural lung conditions

The effect of obstructions within the bronchus itself was identified by LAENNEC [1] as a significant cause of bronchiectasis. Obstruction of the bronchi with foreign objects or tumours is now a relatively rare cause of bronchiectasis. Unsurprisingly most patients with bronchiectasis secondary to retained objects are young children.

Congenital disorders affecting the structure of the bronchial tree can lead to bronchiectasis through a direct effect on the bronchial wall itself, although impaired clearance of sputum through the abnormally dilated structures can further compound the condition.

Williams–Campbell syndrome was first described in 1960 after the case reports of five children were studied by WILLIAMS and CAMPBELL [8]. Histological examination of the bronchial wall revealed a deficiency or absence of cartilage, mostly from the third division of the bronchi down. WILLIAMS and CAMPBELL [8] went on to describe a further 11 children with the same clinical findings of bronchiectasis and cartilage deficiency.

Mounier–Kuhn syndrome (tracheobronchomegaly) is characterised by dilatation of the trachea and large bronchi, usually presenting in young adults. Its underlying pathology is not clearly understood but histological examination has shown atrophy of airway cartilage and smooth muscle.

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GERD: gastro-oesophageal reflux disease; COPD: chronic obstructive pulmonary disease; AAT: α1-antitrypsin deficiency; CFTR: cystic fibrosis transmembrane conductance regulator; ENaC: epithelial sodium channel; ABPA: allergic bronchopulmonary aspergillosis; CVID: common variable immunodeficiency; XLA: X-linked agammaglobulinaemia; CGD: chronic granulomatous disease; Ig: immunoglobulin.
Case reports suggesting an association with Ehlers–Danlos syndrome, and the appearance of the condition in siblings, could point to an unidentified genetic cause for the condition.

**Obstructive airways disease**

To carry on the theme of defects in the gross airway structure itself, perhaps a continuation of this is to consider whether obstructive airways diseases, namely asthma and COPD, could lead to bronchiectasis. It is natural to assume that these conditions would lead to bronchiectasis as both have clearly been shown to cause airway inflammation and structural blockage of airways, either through bronchospasm or fixed airways obstruction, in the case of COPD.

**Asthma**

A number of studies have highlighted the presence of airway remodelling in chronic asthma patients using high-resolution CT (HRCT) scanning techniques. The airway remodelling can vary from mild airway wall thickening to blatant bronchiectasis. Bronchial wall thickening has been found in up to 82% of asthmatic patients in a cohort [9] and in patients with mild asthma [10]. As bronchial wall thickening is indicative of airway inflammation this suggests that a significant number of patients with asthma are at risk of developing bronchiectasis.

The prevalence of bronchiectasis in these studies is estimated at 17.5–40% [9–11]. In the largest of these studies, which comprised of 463 patients with severe asthma, 40% of patients were shown to have evidence of bronchiectasis on HRCT scans [11]. However, study participants were selected for HRCT on the basis of clinical indication, the most common being a suspicion of bronchiectasis. The studies suggest that bronchiectasis is associated with a more severe obstruction and is more apparent in patients who present with a longer history of asthma symptoms, consequently a subgroup of severe asthma patients appear to be at risk of developing bronchiectasis [9–11].

**COPD**

COPD is a term encompassing a number of pathological processes including chronic bronchitis, asthma, emphysema and bronchiectasis. Therefore, it is difficult to fully attribute COPD as the cause of bronchiectasis as in some cases bronchiectasis may be the primary diagnosis. Certainly it is probable that bronchiectasis in COPD is common. A study of moderate-to-severe COPD patients demonstrated the prevalence of bronchiectasis to be 50% [12]. The COPD patients with bronchiectasis were found to have more severe exacerbations and increased sputum inflammatory markers. Further studies are required to elucidate the mechanisms that predispose COPD patients to developing bronchiectasis; severity of airflow obstruction may be a key driver in this mechanism.

**α₁-antitrypsin deficiency**

α₁-antitrypsin (AAT) deficiency is classically associated with predominantly lower lobe emphysema. Bronchiectasis has also been associated with the enzyme deficiency, whether this is a direct consequence of the deficiency or secondary to the emphysema-associated airways obstruction is less clear. In a study of patients with severe AAT deficiency the vast majority of subjects had some evidence of bronchiectasis on a HRCT scan (70 out of 74 subjects), with 27% having clinically significant bronchiectasis with a correlation between forced expiratory volume in 1 second (FEV1) and bronchial wall thickness [13]. In a study of the distribution of AAT alleles in a population of bronchiectasis patients, there was no difference in AAT allele distribution between healthy controls and bronchiectasis patients [14]. However, there was an over representation of hetero- and homozygote AAT deficiency alleles in those patients with bronchiectasis and coexistent asthma. Therefore, the evidence would suggest that AAT deficiency is related to airway obstruction rather than a direct effect of the enzyme deficiency on the bronchial wall structure.
Defects of mucociliary clearance

Ciliary dyskinesia

Abnormalities of cilia structure and/or motility cause a decreased mucus clearance from the lungs. These abnormalities can be due to a primary defect in the structure or function of the cilia or secondary damage to the cilia from external agents, such as bacteria or inhaled noxious agents.

Primary ciliary dyskinesia

Airway cilia are complicated structures containing more than 250 proteins. The ciliary structures are composed of microtubules which are mobilised by structures known as dynein arms, these are divided into two groups the outer and inner dynein arms. This complicated polypeptide structure can be affected by numerous genetic mutations and, as such, primary ciliary dyskinesia (PCD) is a genetically heterogenous disorder. Among the most commonly identified mutations are those of the genes DNAI1 and DNAH5, which code for proteins responsible for the assembly of outer dynein arms.

As cilia are present throughout the body, patients with PCD will often present with multiple symptoms such as sinusitis, recurrent otitis media, infertility and defects of organ lateralisation with situs inversus or situs ambiguus. The triad of bronchiectasis, chronic sinusitis and situs inversus is also known as Kartagener’s syndrome.

Secondary ciliary dyskinesia

A number of noxious agents, both organic and inorganic, have been shown to affect the function of cilia in human airway epithelia. Certain bacteria, such as Pseudomonas aeruginosa and Haemophilus influenzae, have been shown to disable mucociliary clearance by releasing products that inhibit ciliary beat frequency, allowing them to persist and propagate infection [15, 16].

Inhaled inorganic substances such as diesel particles [17] and cigarette smoke [18] have also been shown to have a direct effect on ciliary function, inhibiting ciliary beat frequency. It is important to note here that no causal role for tobacco smoking and the development of bronchiectasis has been made, indeed outside of COPD bronchiectasis appears to be a disease of the nonsmoker.

Aspiration of gastric contents is a well recognised, but perhaps under diagnosed, cause of bronchiectasis. Whilst aspiration of both acid and nonacid stomach contents leads to direct inflammation of the bronchial wall, ciliary function may also be affected by these agents.

Channelopathies

As previously mentioned, the epithelial lining of the airway is coated in a liquid known as the airway surface liquid. It contains two layers, the outer mucus layer and an inner periciliary layer. Ion channels within the apical surface of the epithelial levels regulate the fluid content of this layer to ensure adequate hydration. This enables the cilia to move in a liquid layer but also prevents the desiccation of the mucus into a thick, sticky substance that is difficult to mobilise.

Defects in the ion channels of the epithelial layer can lead to dehydration of the airway surfaces, thereby affecting the depth of the periciliary layer and bringing the cilia into contact with the viscous mucus layer, further impeding its function. The most widely recognised of these defects is that found in CF. Here, the loss of a chloride channel known as the CF transmembrane regulator (CFTR) protein leads to the inability of the epithelial cells to excrete chloride. The dysregulation of the ion transport is further compounded by the effect of CFTR on another ion channel, that of the epithelial sodium channel (ENaC). CFTR is an inhibitor of the ENaC channel and therefore the loss of CFTR is postulated to lead to hyperactivity of the sodium channel, resulting in a large
increase in the transport of sodium into the epithelial cell with a corresponding movement of water out of the airway liquid.

In theory, genetic defects of the ENaC channel could lead to bronchiectasis if such a mutation led to over activity of the channel. Whilst mutations of ENaC genes have been identified in patients with idiopathic bronchiectasis [19], a significant number of these were also carriers of a CFTR mutation. Furthermore, a single CFTR mutation is frequently observed in patients with diffuse bronchiectasis. A study comparing patients with either none, one or two CFTR mutations suggested a continuum of CFTR dysfunction (as measured by nasal potential differences) existed and that this may lead to the development of bronchiectasis in some patients who are CFTR heterozygotes [20].

**Allergic bronchopulmonary aspergillosis**

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary condition caused by a hypersensitivity reaction to the ubiquitous environmental fungus *Aspergillus fumigatus*. It is most commonly seen in patients with pre-existing asthma or CF and is clinically characterised by recurrent wheeze, pulmonary infiltrates and the development of bronchiectasis. The hypersensitivity reaction has mixed features of immediate hypersensitivity (type I), antigen–antibody complexes (type III) and inflammatory cell responses (type IV) [21].

The inflammatory cell response seen in ABPA shows a predominance of T-helper cell type 2 (Th2) cells leading to a release of cytokines mediating allergic inflammation (as opposed to the Th1, cytotoxic pathway) [22]. The type I hypersensitivity reaction causes local degranulation of mast cells and histamine release leading to bronchoconstriction. The combination of airway inflammation, which leads to viscous, eosinophil-laden mucus, plugging and airway obstruction, and bronchospasm leads to a reduction in mucociliary clearance and the development of bronchiectasis. As such bronchiectasis in ABPA is common. In three large case studies it was found that central bronchiectasis was present in 69–76% of patients with ABPA [23–25].

**Immunodeficiency**

Defects in the immune system leave the lungs vulnerable to infection and in some cases the development of bronchiectasis can be the first indication of immunodeficiency.

The most common forms of primary immune deficiencies observed in patients with bronchiectasis are common variable immune deficiency (CVID), X-linked agammaglobulinaemia (XLA) and chronic granulomatous disease (CGD).

**Common variable immune deficiency**

CVID is characterised by reduced levels of immunoglobulins (Igs) with associated recurrent bacterial infections. An increased risk of autoimmune conditions and malignancy has also been identified. The majority of patients present with recurrent pulmonary infections at a mean age 29 years [26]. CVID is the most common primary immune deficiency to cause bronchiectasis. A case series undertaken in a UK population identified 68% of the patients with CVID as having evidence of bronchiectasis [27]. The most likely cause of this high rate of incidence could be the delay in the diagnosis of CVID, with a mean duration of 4 years between reporting of symptoms and diagnosis [27].

**X-linked agammaglobulinaemia**

XLA is caused by a mutation of a tyrosine kinase gene that is involved in the development of B-lymphocytes, leading to an absence of circulating B-lymphocytes and the absence of Igs. Given the severity of the immune deficiency it usually presents much earlier than CVID, usually being diagnosed in early childhood [28]. Despite treatment with replacement Igs, chronic lung disease can still develop with the risk of developing bronchiectasis increasing with age [29].
**Chronic granulomatous disease**

CGD is a group of disorders characterised by a loss of phagocytic NADPH oxidase, without which phagocytes are unable to produce the reactive oxygen species required to kill ingested bacteria. Infections are mainly due to *Staphylococcus aureus*, *Serratia marcescens*, *Salmonella* sp., *Klebsiella* sp. and *Burkholderia cepacia*.

**Antibody deficiency with normal Igs**

In a study of patients with bronchiectasis and normal IgG levels, 11% were shown to have specific antibody production deficiencies with an inability to respond to pneumococcal and *H. influenzae* vaccines [30].

**Secondary immunodeficiency**

The development of bronchiectasis in HIV-infected patients has been noted in a number of case series. While recurrent pulmonary infection is likely to be the major factor in the development of bronchiectasis in these patients, the development of lymphocytic interstitial pneumonia may also be implicated [31].

**Infections**

**Childhood infections**

A number of childhood respiratory infections have been implicated in the pathogenesis of bronchiectasis. The most widely recognised infectious causes of bronchiectasis are measles and pertussis infection in the West [32], with tuberculosis being a major cause elsewhere.

**Nontuberculous mycobacterial infection**

Globally, *Mycobacterium tuberculosis* infection remains a major cause of morbidity and mortality and a significant cause of bronchiectasis. In developed countries with screening programmes and adequate access to treatment, the incidence of new infections remains low. However, the incidence of nontuberculous mycobacterial (NTM) pulmonary infections is increasing. These mycobacteria vary in pathogenecity with *Mycobacterium avium* complex (MAC) being the most pathogenic whilst other organisms, such as *Mycobacterium gordonae* and *Mycobacterium abscessus*, act as opportunistic pathogens and are only found in patients with underlying lung diseases. NTM is commonly present in one of three clinical forms; 1) a tuberculosis-like pattern with a predominant upper lobe fibrocavitatory disease, mostly found in older males with COPD; 2) nodular bronchiectasis, most commonly seen in middle-aged females; and 3) hypersensitivity pneumonitis [33].

The second of these clinical forms is also known as “Lady Windemere syndrome”, and was first described in 1992 in a case series of 29 predominately elderly, female patients [34]. The patients had MAC infection with bronchiectasis predominantly affecting the middle lobe and lingula. The authors postulated that persistent voluntary cough suppression could lead to chronic inflammatory processes in these poorly draining lung regions which are susceptible to MAC infection [34].

**Bronchiectasis in systemic diseases**

**Inflammatory bowel disease**

The development of bronchiectasis in patients with ulcerative colitis is a well recognised phenomenon and the subject of a number of case series [35]. Classically, bronchiectasis develops after resection of the large bowel, suggesting a common immune system response that becomes
concentrated on the bronchial wall after the bowel is removed. The common embryonic origin and similar structures of bowel and bronchial wall (columnar epithelial and submucosal glands) add weight to this theory.

The link between Crohn’s disease and bronchiectasis is less clear with only a small number of case reports detailing their coexistence [36], perhaps too few to determine a definite association.

**Connective tissue diseases**

A number of connective tissue diseases have been noted to be associated with bronchiectasis, largely based on case series reviews of small numbers of patients. The clearest association is that between rheumatoid arthritis and bronchiectasis. Studies have estimated the incidence of bronchiectasis in rheumatoid arthritis patients to be as high as 41% with a significant number of them being asymptomatic [37]. Again no clear pathological process has been identified as the cause of this association, although studies have suggested common genetic predisposition with an association between human leukocyte antigen sub-groups [38]. An effect of the immunosuppressive agents used in rheumatoid arthritis treatment has also been postulated, although a significant number of patients develop bronchiectasis prior to the onset of arthropathy. Associations between bronchiectasis and Sjögren’s syndrome [39], systemic sclerosis [40], systemic lupus erythematosus [41], ankylosing spondylitis [42, 43] and relapsing polychondritis [44] have all been made in small case series reviews.

**Yellow nail syndrome**

Yellow nail syndrome is a rare syndrome that was first described in 1964 by Samman and White [45] and is characterised by bronchiectasis, lymphoedema and a characteristic appearance of the nails. The underlying pathological defect is not clear, although a recent study revealing an association with chronic rhinosinusitis suggests a possible defect in an inflammatory pathway or mucociliary clearance rather than a structural defect within the lung itself [46].

**Idiopathic bronchiectasis**

In two large studies [47, 48], which identified the cause of bronchiectasis in adults, a significant proportion of patients (26% and 53%, respectively) were found to have no identifiable cause and were labelled as having idiopathic bronchiectasis, the majority of whom were found to be female and nonsmokers. As all the patients studied had undergone rigorous clinical testing and their history had been reported, leading to the exclusion of all known causes, including genetic disorders, it is unlikely under recognition of known causes of bronchiectasis could have occurred. Even in paediatric studies, with much shorter follow-up periods and clear exposure histories, no cause could be found for bronchiectasis in 25% of the patients [32]. It is clear, therefore, that there is still much to learn about bronchiectasis and its underlying pathogenesis.

**Statement of interest**

None declared.

**References**


