Bronchiectasis

Rosemary J Boyton

Abstract

Bronchiectasis is defined as irreversible, abnormal dilatation of one or more bronchi, with chronic airway inflammation, associated chronic cough and sputum production, recurrent chest infections and airflow obstruction. The diagnosis of bronchiectasis is made clinically and confirmed by high-resolution computed tomography (HRCT) of the chest. Patients with a diagnosis of bronchiectasis should be referred to a specialist unit for investigation and management. This article deals with non-cystic fibrosis (CF) bronchiectasis. Bronchiectasis is a common structural endpoint that can be reached by several pathological routes from foreign body obstruction to post-infectious damage (tuberculosis), genetic defects (cystic fibrosis), abnormal host defence (ciliary dyskinesia and hypogammaglobulinaemia) and autoimmune disease (rheumatoid arthritis and ulcerative colitis). About half of all cases are called idiopathic since no known underlying cause is identified following detailed investigation. These patients typically have bilateral, predominantly lower lobe disease, and chronic rhinosinusitis. The underlying pathogenesis of bronchiectasis is not known. Innate and adaptive immune mechanisms have been implicated. There appear to be two stages to the disease process: an initial insult followed by a continuing inflammatory process encompassing recurrent infection and progressive lung damage. Abnormalities in immune regulation may predispose to bronchiectasis, both at the time of the initial insult that sets off the disease and during the on-going inflammatory process that ends in progressive lung damage. Immunogenetic evidence suggests a link between the extent of natural-killer (NK) cell activation and disease susceptibility. Further evidence for adaptive immune mechanisms includes a genetic association with HLA-DR1, DQ5 and increased susceptibility to idiopathic bronchiectasis.

Keywords Bronchiectasis; human leukocyte antigen; immunology; infection; killer immunoglobulin-like receptors; lung; natural killer cells; neutrophils; T cells

What's new?

- Recent immunogenetic evidence suggests a link between natural killer (NK) cell activation and disease susceptibility, implicating a predisposing role for innate immune mechanisms
- A genetic association between HLA-DR1, DQ5 and increased susceptibility to idiopathic bronchiectasis is suggestive of a role for adaptive immune mechanisms

Definition

Bronchiectasis is a common structural endpoint with many causes, ranging from foreign body obstruction to post-infectious damage (tuberculosis), genetic defects (cystic fibrosis), abnormal host defence (ciliary dyskinesia and hypogammaglobulinaemia) and autoimmune disease (rheumatoid arthritis and ulcerative colitis). There is irreversible abnormal dilatation of one or more bronchi, with chronic airway inflammation, associated chronic cough and sputum production, recurrent chest infections and airflow obstruction.[1–3]

Epidemiology

The prevalence of bronchiectasis is not known.[1,2] High-resolution computed tomography (HRCT) has led to increased detection, particularly in patients who in the past might have been undiagnosed or classified as chronic obstructive pulmonary disease (COPD). One study found that 50% of patients with a diagnosis of COPD had evidence of bronchiectasis on HRCT thorax.[4] HRCT allows a diagnosis of bronchiectasis in mild cases. Severe bronchiectasis is becoming less common in developed countries, probably because of improved socioeconomic conditions, vaccination against measles and whooping cough, and effective antibiotic therapy. It remains an important cause of childhood morbidity in developing countries. There is an increased incidence of bronchiectasis among specific ethnic groups. The incidence among Alaskan Native children in the Yukon-Kuskokwim region is reported to be about 14 cases per 1000 of the population.[5,6] In children less than 15 years old from New Zealand (NZ), the incidence of non-cystic fibrosis (CF) bronchiectasis is 17.8 in Pacific, 4.8 in Maori, and 1.5 in NZ European children per 100,000 per year.[7] In central Australian Aborigines, the incidence is 14 per 1000.[8] In these populations, bronchiectasis is associated with recurrent respiratory infection in infancy and early childhood. These rates compare with 0.1 per 1000 in Scotland[9] and 4.9 per 1,000,000 in Finnish children.[10] Non-CF bronchiectasis is thought to be more common and more virulent in women.[11]

Pathophysiology

The bronchial airways are weakened by destruction of elastic and muscle layers, leading to abnormal dilatation; this allows mucus to accumulate and favours bacterial infection. The damaged epithelium lacks ciliated cells, which precludes the effective removal of excess mucus. This structural damage promotes chronic microbial colonization and predisposes to recurrent bacterial infections.[1,2]

The Reid classification categorizes bronchiectasis according to pathological and radiological appearance:

- in cylindrical or tubular bronchiectasis there are dilated airways
- varicose bronchiectasis is characterized by focal, constrictive areas along dilated airways

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- in saccular or cystic bronchiectasis there is progressive dilatation of the airways that end in large cysts, saccules or 'grape like' clusters.[1,2]

The underlying pathogenesis of bronchiectasis is not known. It has been proposed that progressive lung damage results from a 'vicious cycle' of recurrent bacterial infection and a poorly regulated inflammatory response (Figure 1).[2] Airway inflammation is characterized by increased tumour necrosis factor α (TNF-α), interleukin-6 (IL-6), IL-8, IL-1α, IL-1β, C5a, and leukotriene B4, and infiltration by neutrophils, $CD4^+$ and $CD8^+$ T cells.[2] It can be caused by an acute insult to the bronchial wall resulting from, for example, childhood whooping cough or inhalation of a toxic gas, leaving a damaged area that subsequently becomes infected. Alternatively, a recognized deficiency of host defence renders the individual prone to infection, as is the case in primary ciliary dyskinesia (PCD) or common variable immune deficiency (CVID). However, in many cases, the starting point of the 'vicious cycle' remains obscure. There appear to be two stages to the disease process: the initial insult, and the on-going inflammatory process that encompasses recurrent infection and progressive lung damage. Abnormalities in immune function and regulation could predispose to bronchiectasis through abnormal responses to the initial insult and the on-going inflammatory process. These are associated with increased susceptibility to specific bacterial, non-tuberculous mycobacterial (NTM), and fungal infections, which end in progressive lung damage (Table 1).

In idiopathic bronchiectasis, there is no defined underlying cause.[1,2,12] Immunogenetic evidence suggests a link between the extent of natural killer (NK) cell activation and disease susceptibility, implicating a predisposing role for innate immune mechanisms.[13,14] This hypothesis is based partly on the finding of bronchiectasis in patients with transporter for antigen presentation (TAP) deficiency syndrome, a rare disease in which impaired human leukocyte antigen (HLA) class I expression encompasses

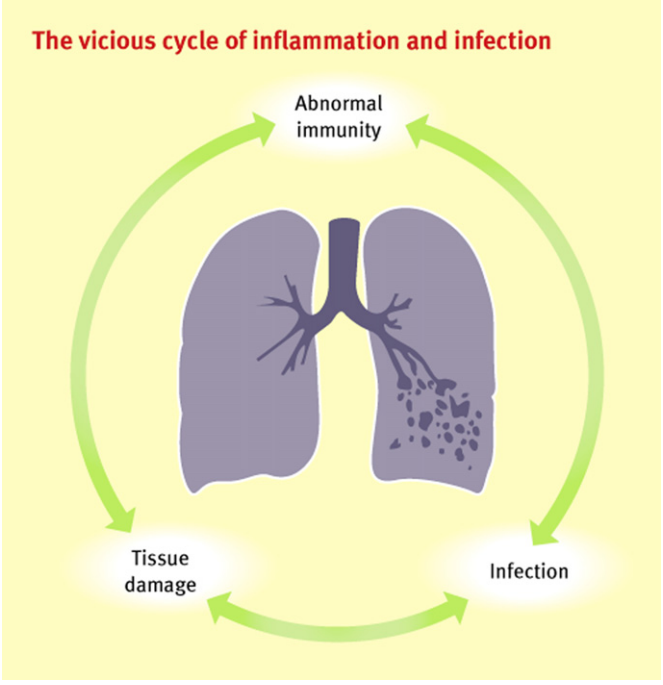

Figure 1

Pathogens associated with exacerbations and disease progression in bronchiectasis

Bacteria

Common

Haemophilus influenzae
Haemophilus parainfluenzae
Pseudomonas aeruginosa

Less common

Streptococcus pneumoniae
Moraxella catarrhalis
Staphylococcus aureus
Stenotrophomonas maltophilia
Gram-negative enterobacter
Non-tuberculosis mycobacteria
Mycobacterium avium complex (MAC)
Mycobacterium kansasii
Mycobacterium chelonae
Mycobacterium fortuitum
Mycobacterium malmoense
Mycobacterium xenopi
Aspergillus-related disease

Table 1

dysregulated NK and γδ cells,[15] and inferred following combinational analysis of HLA-C/KIR genotypes in patients with idiopathic bronchiectasis. High-resolution HLA-C and killer immunoglobulin-like receptors (KIRS) analysis shows that HLA-Cw*03 alleles and HLA-C group 1 homozygosity is associated with an increased risk of idiopathic bronchiectasis.[13,14] Further analysis of the relationship between *HLA-C* and *KIR* genes suggests a shift of balance to activatory NK cell function.

Adaptive immunity likely has a role in idiopathic bronchiectasis, as CD4 and CD8 T cells are found in diseased lung tissue. An association between idiopathic bronchiectasis and HLA-DR1, DQ5 has been reported.[16] Individuals with bronchiectasis are commonly infected with specific bacterial pathogens such as *Haemophilus influenzae*, *H. parainfluenzae*, *Pseudomonas aeruginosa* and *Streptococcus pneumoniae*. It is likely that there is immune response gene variability, in terms of the ability of particular HLA class I and/or class II alleles to present immunodominant epitopes to T cells.

The occurrence of bronchiectasis associated with ulcerative colitis (UC) is rare, but raises challenging questions. Progressive bronchiectasis developing within 1 year of colectomy has been described in patients with UC. A case has been made for a common aetiological link through autoimmune mechanisms between UC and corticosteroid-responsive bronchopulmonary disease. Markers of risk may be identified: a genetic study, relating disease susceptibility to functional polymorphisms in the cytokine IFNγ and the CXC chemokine receptor CXCR1, showed that susceptibility to UC-associated bronchiectasis was associated with IFNγ (+874T/A) and CXCR-1 (+2607G/C) polymorphisms.[17]

Causes of bronchiectasis

Bronchiectasis appears to be a structural endpoint with many different causes and associations (Table 2).[1–3] However, in about

half of all cases no underlying cause is found.[12] These patients typically have bilateral, predominantly lower lobe disease, chronic rhinosinusitis, profound tiredness and difficulty concentrating; they are more commonly female and present with chronic cough and sputum production in adult life.

Clinical features

Symptoms: patients with mild disease may be asymptomatic except during clearly defined exacerbations. The most common symptoms are chronic cough and daily sputum production (typically tenacious and mucopurulent), intermittent haemoptysis, foetor and pleuritic chest pain (usually associated with infective exacerbations), breathlessness, and wheeze. Tiredness with poor concentration, low-grade fever and chronic rhinosinusitis are also clinical features of the disease. Exacerbations, caused by viral and/or bacterial infection, are associated with fever, malaise and increased cough as well as increased sputum volume and purulence.

Signs: there may be coarse inspiratory and expiratory crackles on auscultation and airflow obstruction with wheeze. There may be signs of right heart failure and/or respiratory failure in severe disease. Finger clubbing is seen only in severe disease (usually cystic bronchiectasis).

Diagnosis

The diagnosis is usually clinical, confirmed with HRCT of the chest.

Investigations

Investigations should aim to confirm the diagnosis, identify any treatable cause of the bronchiectasis and optimize management to reduce the frequency and severity of exacerbations and lung damage (Table 3).[1,2]

Chest radiographs are insensitive at detecting bronchiectasis (at about 50%) making HRCT chest the investigation of choice. HRCT is 97% sensitive at detecting disease. Chest radiographs may show 'tramlines', indicating thickened airways, 'ring shadows', and segmental or lobar collapse. The characteristic changes seen on HRCT in bronchiectasis are:

- tramlines (non-tapering of bronchi)
- the 'signet-ring' sign (end-on dilated bronchi larger than accompanying pulmonary artery)
- crowding of the bronchi with associated lobar volume loss
- mucous plugging of dilated bronchi (flame and blob sign)
- thickening and plugging of small airways resulting in numerous nodular and V- or Y-shaped opacities.[18]

Expiratory scans show post-obstructive air trapping, indicative of small airways disease.[18] Varicose bronchiectasis has a beaded or 'tree in bud' appearance, while cystic (or saccular) bronchiectasis is seen as thin-walled cystic spaces that may contain fluid levels.

Management

The goal of treatment is to prevent or slow down progressive lung damage. This entails treating any predisposing medical conditions, controlling symptoms, reducing the frequency and severity of infective exacerbations, and dealing with complications early. If bronchiectasis is suspected clinically, or confirmed by HRCT, the patient should be referred for further investigation and specialist management.

Every patient should have a self-management plan for exacerbations and intercurrent maintenance that they have discussed with their doctor and clinical nurse specialist.

Causes of bronchiectasis

Idiopathic

Postinfectious
- Bacteria — *Bordetella pertussis* — whooping cough
- *Mycobacterium tuberculosis*
- Non-tuberculous mycobacteria
- *Aspergillus* species (allergic bronchopulmonary aspergillosis)

Virus (adenovirus 3, 7 and 21, measles virus, influenza virus, human immunodeficiency virus)

Mucociliary clearance defects
- Primary ciliary dyskinesia
- Cystic fibrosis
- Young's syndrome (azoospermia)

Sequelae of toxic inhalation, aspiration or local bronchial obstruction
- Toxic gases (e.g. chlorine, ammonia)
- Overdose (e.g. intravenous heroin)
- Foreign body
- External compression
- Smoke inhalation

Immunodeficiency
- Primary (hypogammaglobulinaemia, transporter for antigen presentation (TAP) deficiency syndrome)
- Secondary

Malignancy (e.g. chronic lymphatic leukaemia), chemotherapy, or immune modulation (after transplantation)

Autoimmune conditions
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sjögren's syndrome
- Relapsing polychondritis
- Inflammatory bowel disease (ulcerative colitis and Crohn's disease)

Congenital conditions
- Tracheobronchomegaly (Mounier–Kuhn syndrome)
- Cartilage deficiency (Williams–Campbell syndrome)
- Marfan's syndrome

Other
- Yellow nail syndrome
- α1-antitrypsin deficiency
- Mercury poisoning
- Fibrosis (fibrosing alveolitis, sarcoidosis, post-irradiation)

Table 2

Investigations in bronchiectasis

Radiology

- Chest radiograph
- Sinus radiograph
- High-resolution thin-section CT thorax

Lung function tests

- Arterial blood gas
- Exercise capacity
- Static lung volumes and transfer factor for carbon monoxide
- Flow-volume loop, spirometry/reversibility

Sputum

- Microscopy, culture and sensitivities
- Smear and culture for acid-fast bacilli
- Persistent isolation of *Staphylococcus aureus* in sputum should alert to the possibility of allergic bronchopulmonary aspergillosis or cystic fibrosis (CF)

Blood tests

- Full blood count with differential white cell count
- Erythrocyte sedimentation rate (ESR)
- C-reactive protein (CRP)
- Total immunoglobulin (Ig) levels of IgG, IgM, IgA, IgE
- Baseline specific antibody levels to tetanus toxoid and the capsular polysaccharides of *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. Immunization with the appropriate vaccine followed by repeat specific antibody level responses after 21 days if baseline levels are low
- Investigations to exclude CF — measurement of sweat chloride and *CFTR* genetic mutation analysis
- *Aspergillus* radioallergosorbent test (IgE) and precipitins (IgG)
- Rheumatoid factor
- Protein electrophoresis
- α1-antitrypsin

Other

- ECG
- Echocardiography
- Skin tests (atopy, *Aspergillus*)
- Sweat test, nasal potentials, CF genotyping
- Cilia studies (if nasal mucociliary clearance is prolonged or nasal nitric oxide low, proceed to light microscopy of ciliary beat frequency and then electron microscopy)

Selected patients

- Fibreoptic bronchoscopy
- Videofluoroscopy of swallowing to identify aspiration
- pH study for acid reflux
- Semen analysis
- Tests for rare immunodeficiencies (e.g. neutrophil and lymphocyte function studies)
- Tests for related conditions where clinically indicated

Table 3

Physiotherapy

Physiotherapy is fundamental in the management of bronchiectasis, to reduce the severity and progression of disease. All patients should be taught techniques that promote airway clearance on a daily basis. These include:

- postural drainage
- active cycle-of-breathing techniques
- cough augmentation (using flutter valves)
- exercise regimens (to prevent general deconditioning).

During acute infective exacerbations, the physiotherapist assists in clearing tenacious sputum.

Airflow obstruction should be treated with short- and long-acting bronchodilators and/or inhaled corticosteroids. The bronchodilator response should be assessed before starting treatment. Pneumococcal and influenza vaccinations should be considered unless there is a contraindication. Nutrition should be optimized and referral to a dietitian considered. Low mood, depression and anxiety are relatively common in this chronic illness and should be looked for and addressed. Surgery can be curative in patients with isolated lobar bronchiectasis with no underlying predisposing cause for generalized bronchiectasis. It may also be indicated in life-threatening haemoptysis that has not responded to bronchial artery embolization. Referral for lung transplantation may be appropriate when severe disease progresses despite optimal medical management. Non-invasive ventilation can be beneficial in chronic respiratory failure secondary to bronchiectasis.

Underlying conditions

The identification and treatment of predisposing medical conditions is important. For example, treating reflux if there is evidence of recurrent aspiration. CVID or hypogammaglobulinaemia is the most common immune deficiency linked to bronchiectasis and these patients benefit from intravenous immunoglobulin therapy, administered every 3 weeks under the guidance of a clinical immunologist. There are no specific treatments for primary ciliary dyskinesia. Attention should focus on the importance of daily physiotherapy and prompt treatment of infective exacerbations.

Worldwide, tuberculosis is a common cause of bronchiectasis that should be identified and treated. There is also a subgroup of patients, more often female, that typically present in middle/old age with evidence of bronchiectasis in the middle lobe or lingula and nodular densities, in whom *Mycobacterium avium* complex is often cultured from sputum samples and is thought to be driving the disease as opposed to colonizing the damaged lung.[19] Rifampicin and ethambutol are included in most recommended regimens due to their synergistic effect. Macrolide and quinolone antibiotics are useful in combination regimens. However, despite prolonged courses of up to 2 years, relapse is common and tolerance of medication is often poor.

Allergic bronchopulmonary aspergillosis (ABPA) is caused by a hypersensitivity reaction to *Aspergillus*, and often leads to upper lobe and proximal bronchiectasis. Treatment is aimed at immune modulation and reduction in inflammation. Oral corticosteroids improve serological tests, pulmonary infiltrates and asthma symptoms. The azoles inhibit ergosterol synthesis in the fungal cell wall membrane, preventing growth, and itraconazole is beneficial in corticosteroid-dependent ABPA.[20] The optimal dose and length of treatment is not defined. Itraconazole is poorly absorbed orally

and new azoles such as voriconazole and posaconazole, with improved minimum inhibitory concentrations (MIC) against several *Aspergillus* species, are being investigated in ABPA.

Acute infective exacerbation

Patients present with increased sputum volume, breathlessness, cough, malaise, and pleuritic chest pain. Antibiotic therapy should be altered based on microbiological results. Common bacterial pathogens causing infective exacerbations are *H. influenzae, H. parainfluenzae* and *S. pneumoniae* (Table 1). First-line therapy, if there is no history of *P. aeruginosa*, should be 14 days' treatment with β-lactam antibiotics (amoxicillin) or, where β-lactamase-producing strains are suspected, co-amoxiclav. Alternative oral agents such as macrolides and quinolones have good penetration into the bronchial mucosa. Moxifloxacin, an 8-methoxyquinolone, has broad-spectrum coverage with improved activity against atypicals, Gram-positive and anaerobic organisms compared with other quinolones while retaining good Gram-negative cover. Where *P. aeruginosa* is thought to be involved, ciprofloxacin is the antibiotic of choice, being the only oral antibiotic that provides significant cover against this organism.

Intravenous antibiotics may be required if the patient fails to improve after oral antibiotics, if oral antibiotics are unsuitable due to the severity of the presenting illness, or if the patient has *P. aeruginosa* resistant to ciprofloxacin. Once again, antibiotic therapy should be tailored to the results of sputum cultures where possible. In the absence of *P. aeruginosa*, second- (cefuroxime) or third-generation (ceftriaxone) cephalosporins or co-amoxiclav are suitable.[21] Where *P. aeruginosa* is present, ceftazidime, carbapenems or tazobactam can be used.[21] Intravenous therapy is continued for 10 days. Aminoglycosides may be added as they have a synergistic effect with β-lactams against *P. aeruginosa*. However, aminoglycoside therapy requires careful monitoring of plasma concentration. Dizziness or balance problems suggesting early ototoxicity should be taken very seriously as there is a cumulative dose effect; the aminoglycoside should be stopped and audiometry arranged. Intravenous therapy does not necessitate prolonged inpatient admission if insertion of a long line and training in self-administration of intravenous antibiotics can be arranged. Patients can then complete treatment at home under the supervision of the home care team.

Prophylactic therapy

Prophylactic antibiotics should be considered in patients with frequent relapses necessitating courses of oral antibiotics (more than six per year), or hospital admissions for intravenous antibiotics (more than twice a year), or patients who relapse within 1 month of appropriate intravenous antibiotic therapy without an explanation.[21] Initially, these patients should be investigated to establish if there is an underlying cause. This might include HRCT, lung function tests, sputum microscopy, culture and sensitivities, smear and culture for acid-fast bacilli and *Aspergillus* serology, depending on the clinical presentation. In our specialist unit, we currently use azithromycin (250 mg) on alternate days after loading.[21] Alternative antibiotics that can be used in patients without *P. aeruginosa* are amoxicillin and doxycycline. The aim is to reduce the frequency, severity and duration of infective exacerbations and produce a period of clinical stability. Long-term ciprofloxacin should be avoided so as not to encourage antibiotic resistance. In secondary prophylactic treatment of patients with *P. aeruginosa*, nebulized colomycin (1–2 MU 12-hourly) is used.[21] Patients should undergo a colomycin trial to check that lung function tests pre- and post-colomycin do not demonstrate a significant (>15%) drop in forced expiratory volume in 1 second (FEV_1). Patients should be reviewed with repeat lung function tests after 3 months. Where prophylactic therapy does not help, a minority of patients benefit from repeat courses of cyclical intravenous antibiotic therapy (commonly every 8–12 weeks).

Eradication therapy for *P. aeruginosa*

P. aeruginosa is associated with a poorer prognosis in bronchiectasis, with more rapid decline in lung function.[22] In view of this, some units attempt to eradicate *P. aeruginosa* at first isolation to prevent chronic colonization. It remains to be seen if this approach is beneficial. In our unit, patients are initially treated with a 2-week course of ciprofloxacin, assuming that the organism is sensitive. If *P. aeruginosa* is recultured following this, the patient is admitted for a 10-day course of intravenous antibiotic treatment, followed by 1 month of nebulized colomycin and 2 weeks of oral ciprofloxacin on discharge home.[21] At the time of writing there is no evidence from controlled studies to support this approach.

The British Thoracic Society has produced detailed guidelines on the management of non-CF bronchiectasis.[23] ◆

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Practice points

- Bronchiectasis is irreversible abnormal dilatation of one or more bronchi, with chronic airway inflammation, associated chronic cough and sputum production, recurrent chest infections, and airflow obstruction
- A diagnosis of bronchiectasis is usually made clinically and confirmed by high-resolution computed tomography (HRCT) of the chest
- Progressive lung damage results from a 'vicious cycle' of recurrent bacterial infection and a poorly regulated inflammatory response
- Patients should be encouraged to perform daily physiotherapy/exercise and take prompt antibiotic treatment for infective exacerbations
- Some patients may benefit from the use of prophylactic antibiotics