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Bronchiectasis

Bronchiectasis is essentially an anatomical diagnosis. It refers to the abnormal and permanent dilatation of one or more central or medium-sized bronchi that is associated with bronchial wall thickening. Although bronchiectasis can be diagnosed by plain radiography of the chest, this is insensitive and usually it is confirmed on axial high resolution computed tomography. For bronchiectasis to be clinically relevant there should be symptoms of chronic airway disease related to the dilated airways but some patients might only experience these at times of exacerbations. This article summarizes the knowledge required by doctors in training for the recognition and management of adult non-cystic fibrosis bronchiectasis.

Epidemiology

The incidence of bronchiectasis is increasing and a study in the UK has estimated it to be 32 per 100 000 person years at risk (Quint et al, 2012). This may be the result of improved identification of cases with more regular use of high resolution computed tomography but highlights the continuing relevance of bronchiectasis in industrialized nations. The prevalence of bronchiectasis increases with age and is rising as the mean age of the population rises. Additionally, there has been an increase in disease burden measured by the rising rate of hospitalizations associated with bronchiectasis (Seitz et al, 2010).

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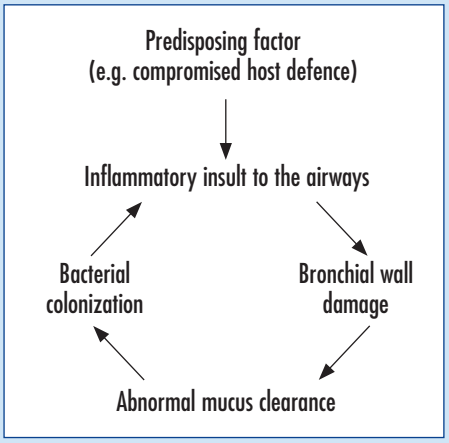
In 2011 the overall prevalence of bronchiectasis in the UK was 227 per 100 000 men and 309 per 100 000 women, peaking in men ≥80 years and woman >70 years of age (Quint et al, 2012). The mortality rate of bronchiectasis patients is varied; a UK study with a 13-year follow-up period and a study from Turkey with 4 years of follow up reported mortality rates of 29.7% and 16% respectively (Onen et al, 2007; Loebinger et al, 2009). Increasing age, worsening lung function, increasing bronchiectasis severity, *Pseudomonas aeruginosa* colonization and low body mass index have all been associated with an increased risk of death while vaccination and regular scheduled physician visits in secondary care have been associated with improved survival (Onen et al, 2007; Loebinger et al, 2009).

Pathogenesis

The abnormally dilated bronchi of bronchiectasis are caused by destruction and weakening of the bronchial wall as a result of inflammation stimulated by a primary inflammatory lung disease (e.g. rheumatoid arthritis) or by infection. Bronchial wall damage results in a vicious cycle of inflammation and injury, known as Cole's vicious cycle hypothesis (McShane et al, 2013); damaged bronchi lose their functional ability to clear mucus resulting in bronchial infection, which in turn stimulates further inflammation and bronchial wall damage that promotes further infection (*Figure 1*).

Figure 1. Vicious cycle hypothesis.



Diagnosis

The criteria for the diagnosis of bronchiectasis include identifying anatomical bronchiectasis and the presence of symptoms associated with chronic airway disease that are caused by the abnormal bronchial dilatation. Anatomical bronchiectasis is characterized on computed tomography scans by the internal diameter of the bronchi being larger than the accompanying blood vessel or where the bronchus fails to taper in the periphery of the chest (*Figure 2*). Three different types of bronchiectasis patterns have been described (Reid, 1950):

1. Cylindrical – uniformly dilated bronchi
2. Varicose – irregularly dilated bronchi resembling varicose veins
3. Saccular – dilated bronchi ending as blind sacs without distal bronchial airways.

The classical clinical presentation of bronchiectasis is that of a suppurative lung disease with daily cough productive of mucopurulent sputum that is often expectorated in large volumes; occasionally, this may be associated with haemoptysis, particularly during infective exacerbations. Other symptoms include dyspnoea, pleuritic chest pain, wheeze, fatigue and weight loss. Some patients will have a chronic dry cough with no regular sputum production, even during exacerbations.

Features that should lead the clinician to suspect bronchiectasis are listed in *Table 2*. A minority of patients have quiescent disease and only experience symptoms during periods of acute infection. Others will have chronic disease with daily sputum production and periodic exacerbations caused by worsening bacterial infection. During an exacerbation the patient may experience increased sputum production, a change in the colour or viscosity of the sputum, haemoptysis, dyspnoea, pleuritic chest pain, wheeze and fatigue; in contrast to pneumonias, fever is not common. Most patients with bronchiectasis either do not have progressive disease or only show slow changes in anatomical damage with time. However, some patients have more rapidly progressive disease that can cause distal small airways obstruction, gradually worsening obstructive lung function, and eventually type 2 respiratory failure and death (Wilson et al, 1997).

The clinical features on examination most commonly include crackles, wheeze and squeaks on auscultation over the site of the affected chest, most commonly both bases but not infrequently the distribution is asymmetrical or mainly apical. Crackles are usually coarse and can shift with coughing; they are thought to be the result of the pooling of secretions within the dilated bronchi. Wheezing may be localized or scattered and may be the result of destruction of the bronchial walls causing collapsibility of the airways, small airways obstruction caused by severe disease or associated airway diseases such as chronic obstructive pulmonary disease, asthma or allergic bronchopulmonary aspergillosis. Clubbing is only present in 2–3% of patients with bronchiectasis, more frequently those with severe disease (King et al, 2006). Patients with mild disease may have no clinical signs.

Aetiology

There are many causes of bronchiectasis (*Table 1*) but despite extensive investigations a cause is not always found and idiopathic bronchiectasis remains the most common diagnosis (26–53%) (Pasteur et al, 2000; Shoemark et al, 2007). The proportion of patients with idiopathic bron-

Figure 2. Computed tomography scan of the chest demonstrating bronchiectasis. a. Gross saccular bronchiectasis. b. Cylindrical bronchiectasis with signet ring sign (arrow).

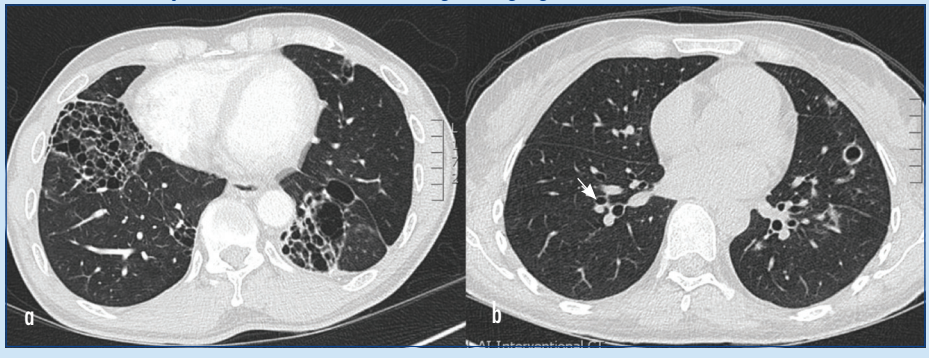


Table 1. Mechanisms and aetiology of bronchiectasis

Congenital anatomical or connective tissue defects	Tracheobronchomegaly (Mounier–Kuhn syndrome)
	Cartilage deficiency (Williams–Campbell syndrome)
	Ehlers–Danlos syndrome
	Marfan's syndrome
Physical obstruction	Tumour
	Foreign body
	Lymphadenopathy
Congenital and acquired immunodeficiencies	Immunoglobulin deficiency*
	Human immunodeficiency virus
	Functional neutrophil defects
	Job's syndrome (hyper IgE syndrome)
Impaired mucociliary clearance	Primary ciliary dyskinesia
	Young's syndrome†
	Cystic fibrosis
Post-infective	Tuberculosis
	Non-tuberculous mycobacteria
	Pneumonia
	Measles
	Whooping cough
	Adenovirus
	Swyer–James syndrome‡
Autoimmune disease	Rheumatoid arthritis
	Sjögren's syndrome
	Systemic lupus erythematosus
	Ankylosing spondylitis
	Relapsing polychondritis
	Inflammatory bowel disease
	Sarcoidosis
	Pulmonary graft *vs* host disease post-stem cell transplant
Airway inflammation	Chronic obstructive pulmonary disease
	Alpha-1 anti-trypsin deficiency
Physical airway injury	Aspiration
	Toxic inhalation, e.g. smoke
Other	Yellow nails syndrome ¶

*common variable immune deficiency and selective immunoglobulin deficiency, myeloma, chronic lymphocytic lymphoma, post stem cell transplantation; †bronchiectasis, sinusitis, azoospermia; ‡ post-infectious obliterative bronchiolitis; ¶ yellow nails, lymphoedema and pleural effusions.
Adapted from Pasteur et al (2010), McShane et al (2013)

chiectasis will depend on the cohort being investigated, and in specialist centres which perform systematic diagnostic evaluations the incidence of idiopathic bronchiectasis is much lower (McShane et al, 2012). Of the identified causes, post-infectious aetiologies and causes of immune dysfunction are the most common (Pasteur et al, 2000; McShane et al, 2012).

At the initial visit it is important to focus the history on a few features that may help identify the potential aetiology. These include the age at symptom onset (to look for congenital causes such as cystic fibrosis or primary ciliary dyskinesia), history of childhood infections or previous severe respiratory tract infections, history of recurrent rhinosinusitis, middle ear infections or history of infertility (primary ciliary dyskinesia or cystic fibrosis), symptoms of variable airflow obstruction (suggestive of allergic bronchopulmonary aspergillosis), symptoms of gastro-oesophageal reflux disease (aspiration), lower gastrointestinal tract symptoms (inflammatory bowel disease) or joint disease (rheumatoid arthritis, and other autoimmune disease). Bronchiectasis may also be associated with other respiratory disease such as asthma and chronic obstructive pulmonary disease and causation is often difficult to establish. Initial investigations that should be carried out are listed in *Table 3*. In addition, where the history suggests a specific aetiology then further investigations should be carried out as listed in *Table 4*.

Microbiology

As the disease progresses the spectrum of pathogens identified in the airways evolve; patients with more severe disease are frequently colonized with pathogens that are particularly difficult to treat as a result of natural or rapidly acquired resistance to antimicrobials. Furthermore, main pathogens commonly found in bronchiectasis form biofilms that render antimicrobials inefficient and protect the organisms from host defence mechanisms (e.g. phagocytosis by innate immune cells). Gram-negative bacteria are the most commonly isolated pathogens from patients with non-cystic fibrosis bronchiectasis.

Frequently isolated pathogens are listed in *Table 5*. The most prevalent include *Haemophilus influenzae*, *P. aeruginosa* and *Moraxella catarrhalis*. *Streptococcus pneumoniae* and *Staphylococcus aureus* are the most common Gram-positive organisms identified in bronchiectasis patients. If *S. aureus* is cultured from sputum this should prompt the clinician to have a high index of suspicion for the diagnosis of cystic fibrosis (Hubert et al, 2004). *P. aeruginosa* is perhaps the most important pathogen in these patients because of its natural resistance to most oral antibiotics, and because *P. aeruginosa* isolation from sputum is associated with decreased lung function (Davies et al, 2006), more frequent exacerbations and inferior quality of life (Wilson et al, 1997).

A. fumigatus is an ubiquitous environmental fungus that may be cultured from some patients suggesting a diagnosis of allergic bronchopulmonary aspergillosis. Non-tuberculous mycobacteria are also commonly isolated from sputum from patients with bronchiectasis, most commonly *Mycobacterium avium* complex. Other commonly identified non-tuberculous mycobacteria are *M. kansasii* and *M. fortuitum*. Non-tuberculous mycobacteria infections are classically associated with elderly, underweight women, affecting the middle lobe, and have been described as Lady Windermere's syndrome (Reich and Johnson, 1992; Mirsaeidi et al, 2013).

Management

The goal of therapy in bronchiectasis is to prevent infective exacerbations and to treat these rapidly and adequately when they occur. This will reduce inflammation and injury in the airways, breaking the vicious cycle. Furthermore, therapy aims to reduce symptoms, prevent lung func-

Table 2. When to suspect bronchiectasis

Recurrent attacks of acute bronchitis that respond to antibiotics		
Positive sputum cultures for:	Single isolate for:	*Pseudomonas aeruginosa*, *Aspergillus fumigatus*, non-tuberculous mycobacteria
	Multiple isolates for:	*Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pneumoniae* and *Staphylococcus aureus*
An episode of major haemoptysis or recurrent haemoptysis		
Persistent audible crepitations in the chest (usually coarse and may shift with coughing)		

Table 3. Initial investigations

Investigation	Reason
Chest radiograph	Baseline for future comparison
	Abnormal in <50% of patients with bronchiectasis
High resolution computed tomography of the chest	Diagnostic
	Evaluate the extent of the disease
	Baseline for evidence of progressive disease
Lung function tests	Baseline for future monitoring
Full blood count (eosinophil count)	Baseline for monitoring of inflammation, eosinophilia may indicate presence of allergic bronchopulmonary aspergillosis or asthma
Erythrocyte sedimentation rate or C-reactive protein	Baseline for monitoring of inflammation
Serum immunoglobulins (IgG, IgM, IgA)	To identify humoral immune deficiencies
Serum IgE	To identify allergic bronchopulmonary aspergillosis (very high levels)
Sputum culture	To identify bacterial, mycobacterial and fungal colonization as well as antimicrobial sensitivities
Aspergillus fumigatus skin prick sensitivity test or specific-IgE and IgG	To identify allergic bronchopulmonary aspergillosis (positive skin prick test, high levels of IgE)

adapted from Pasteur et al (2010)

tion decline and maintain quality of life. If an underlying or modifiable cause of the bronchiectasis is identified then this should be treated promptly to halt disease progression. Additionally, patients should receive a comprehensive therapeutic strategy that includes airway clearance, treatment and prevention of infective exacerbations, and vaccination. Smoking exacerbates symptoms, and active smokers with bronchiectasis should be offered smoking cessation advice. Patients with impaired lung function should be offered pulmonary rehabilitation.

Airway clearance

The aim of pulmonary hygiene is to mobilize airway secretions and eliminate mucus stasis that promotes bacterial outgrowth, inflammation and injury. Expectoration and mucus clearance are enhanced by physiotherapy exercises performed by the patient or his/her relative(s), including postural drainage, manual chest percussion, and active cycling breathing with huff coughs.

Respiratory physiotherapists have an important role in the management of bronchiectasis, as chest clearance techniques seem to be effective in reducing exacerbations and improving quality of life but need to be tailored to the patient's needs. Occasionally chest clearance is assisted by mechanical devices such as oscillatory positive expiratory pressure devices or high-frequency chest wall oscillation, or by inhaled mucolytics.

Mucolytics decrease sputum viscosity making it easier to clear mucus from the airway. Nebulized isotonic (0.9%) or hypertonic (6% or 7%) saline are frequently used to reduce airway inflammation (Reeves et al, 2011) and improve sputum expectoration, lung function and quality of life (Kellett and Robert, 2011). The effects on outcomes of isotonic and hypertonic saline appear to be similar (Nicolson et al, 2012).

Recombinant human DNAse is effective in the management of cystic fibrosis bronchiectasis, but in non-cystic fibrosis bronchiectasis was associated with worse outcomes in a clinical trial, including increased frequency of exacerbations, hospitalizations and worse lung function decline (O'Donnell et al, 1998). Therefore, recombinant human DNAse should not be given to patients with non-cystic fibrosis bronchiectasis. Inhaled dry powder mannitol has the ability to improve the tenacity of sputum but at present its use is not recommended because of a lack of evidence demonstrating improved clinical outcomes (Bilton et al, 2013).

Antibiotic therapy

Treatment of acute exacerbations

The antibiotics used in the treatment of exacerbations are dictated by the patient's sputum cultures (including acid-fast bacteria). Hence it is important to obtain sputum cultures at baseline and before initiating antibiotic therapy. In patients with milder disease and in whom culture results are not available exacerbations may be treated with antibiotics that are effective against many *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* strains, e.g. amoxicillin, doxycycline or clarithromycin.

If symptoms do not resolve with these, or the patient is infected with an organism

Table 4. Additional investigations

Investigation	When		Suspected diagnosis
Sodium sweat test or cystic fibrosis transmembrane conductance regulator genetic mutation analysis	Family history <40 years of age and no cause identified or presence of:	Upper lobe bronchiectasis	Cystic fibrosis
		Symptoms of malabsorption	
		Infertility	
		Staphylococcus aureus in sputum	
Nasal saccharin test or exhaled nitrous oxide	Symptoms since childhood, recurrent rhinosinusitis and otitis media, male infertility, dextrocardia, family history		Primary ciliary dyskinesia (Kartagener's syndrome)
Bronchoscopy	Localized disease on high resolution computed tomography		Bronchial obstruction
Oesophageal and videofluoroscopy swallowing studies	Bibasal disease with symptoms of reflux or aspiration		Aspiration
Gastrointestinal investigations (gastroscopy and colonoscopy)	Lower gastrointestinal tract symptoms		Inflammatory bowel disease
HIV test	Additional HIV associated infections, presence of HIV risk factors		HIV/AIDS
Alpha-1 antitrypsin (A1AT) levels	Family history of A1AT deficiency, lower zone emphysema, emphysema in the absence of risk factors (e.g. smoking) or <45 years		A1AT

adapted from Pasteur et al (2010)

Table 5. Pathogens identified in sputum of patients with non-cystic fibrosis bronchiectasis

	Isolated pathogens		Colonizing pathogens
Pathogen cultured from sputum	Macfarlane et al (2010)*	King et al (2006)†	Macfarlane et al (2010)‡
Haemophilus influenza	52%	47%	33%
Pseudomonas aeruginosa	43%	12%	35%
Streptococcus pneumoniae	30%	7%	9%
Coliforms	30%	4%	9%
Moraxella catarrhalis	27%	8%	6%
Staphylococcus aureus	24%	4%	8%
Aspergillus spp.	9%	2%	2%
Non-tuberculous mycobacteria	3%	2%	0.7%

* isolated pathogen one or more times from a patient within 1 year; † isolated at first presentation; ‡ cultured on at least two occasions, 3 months apart within 1-year period

resistant to macrolides or amoxicillin, or the patient develops another exacerbation within a short time, then a course of co-amoxiclav is recommended. Patients with suspected *P. aeruginosa* infection (e.g. those with a previous positive sputum culture for *P. aeruginosa* or with severe disease) should be treated with oral ciprofloxacin, which is the only standard oral antibiotic that is effective against *P. aeruginosa*.

For those that remain unwell, or are colonized with *P. aeruginosa* that are resistant to ciprofloxacin, intravenous monotherapy with an anti-pseudomonal antibiotic is recommended, e.g. either an anti-pseudomonal penicillin (e.g. tazobactam-piperacillin), a third-generation cephalosporin (e.g. ceftazidime), an aminoglycoside (e.g. gentamycin or tobramycin), or monobactams. Combination intravenous therapy is nowadays largely reserved for patients with *P. aeruginosa* that are resistant to at least one anti-pseudomonal agent or do not respond to intravenous monotherapy (Elphick and Tan, 2005).

The optimum duration of antibiotic therapy is not clearly defined. Patients with mild or moderately severe disease that only causes infrequent exacerbations could be treated for 7–10 days; patients with more severe disease, *P. aeruginosa* infection or frequent exacerbations should receive treatment for 10–14 days (Murray et al, 2009; Pasteur et al, 2010). The management of non-tuberculous mycobacteria infections and other less common resistant organisms is complex and beyond the scope of this article.

Prevention of exacerbations

Although the potential benefits of preventing long-term colonization with *P. aeruginosa* are not clear, the initial identification of *P. aeruginosa* in patients with non-cystic fibrosis bronchiectasis in sputum can prompt an attempt to eradicate the organism from the airways as this may reduce associated increases in airway inflammation and exacerbation frequency (Chalmers et al, 2012; White et al, 2012). The recommended strategy for *P. aeruginosa* eradication is 2 weeks of oral ciprofloxacin 750 mg twice a day; if this fails then another 4 weeks of oral ciprofloxacin could be given in combination with an inhaled antibiotic (e.g. tobramycin, gentamycin or colomycin) or 2 weeks of intravenous anti-pseudomonal antibiotics (Pasteur et al, 2010).

Patients who have three or more exacerbations per year or with progressive deterioration in lung function may be suitable for prolonged prophylactic antibiotic therapy to prevent exacerbations and slow lung function decline (Pasteur et al, 2010). The potential benefit of prophylactic antibiotic therapy needs to be assessed for each individual patient and weighed against the risk of possible adverse events. For patients not known to be colonized with *P. aeruginosa* long term or rotating courses of low dose amoxicillin, doxycycline or coamoxiclav (Pasteur et al, 2010), although as a result of the lack of evidence for the use of 'rotational antibiotics', the use of macrolides to reduce exacerbation frequency is preferred (see below). For patients with known or suspected *P. aeruginosa* colonization airways infection can be suppressed and exacerbation frequency reduced by 'off-label' treatment with nebulized colomycin or aminoglycosides (Couch, 2001; Murray et al, 2011).

Pneumococcal and influenza vaccination is given to patients with bronchiectasis, as they are recommended for patients with chronic respiratory disease.

Anti-inflammatory therapy

Evidence for the use of conventional corticosteroid anti-inflammatory therapy in the management of bronchiectasis is lacking, and these drugs have various adverse effects as well as suppressing immune function that may predispose to further infection. Oral corticosteroids are therefore generally only used in the treatment of exacerbations in patients with airflow obstruction (e.g. asthma and chronic obstructive pulmonary disease) or long term in patients with allergic bronchopulmonary aspergillosis, and inhaled steroids for patients with associated asthma (Kapur et al, 2009).

Azithromycin has immunomodulatory and anti-inflammatory properties and is used in a select group of patients with frequent exacerbations and chronic symptoms. In bronchiectasis azithromycin given daily (250 mg) or three times weekly (500 mg) reduces exacerbation frequency, improves quality of life and decreases sputum production (Wong et al, 2012). Before initiating long-term azithromycin therapy it is important to obtain sputum cultures to rule out non-tuberculous mycobacteria and avoid the development of macrolide-resistant non-tuberculous mycobacteria. Additionally, an electrocardiogram should be performed to evaluate the QT interval and medication interactions should be reviewed to minimize the risk of QT interval prolongation. Treatment with long-term azithromycin can cause abnormal liver function, tinnitus and hearing loss, so these need careful monitoring.

Surgery

Patients with disease localized to a single lobe or perhaps a single lung that have ongoing symptoms and frequent exacerbations despite maximal medical therapy may be referred for lobectomy or segmentectomy, which is associated with low perioperative morbidity and mortality (Mitchell et al, 2012). The other main indication for surgery for bronchiectasis is to resection of the source of bleeding in life-threatening haemoptysis; bronchial artery embolization is an effective alternative therapy to surgery for major haemoptysis. BJHM

KEY POINTS

- Bronchiectasis is an anatomical diagnosis but the presence of symptoms is required for clinical relevance.
- It is important to investigate for possible causes of bronchiectasis as treating these has a significant effect on outcome.
- The management of bronchiectasis should involve a multidisciplinary approach and a comprehensive therapeutic strategy that includes airway clearance, treatment and prevention of infective exacerbations, pulmonary rehabilitation, vaccination and smoking cessation.

Conflict of interest: none.

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Further reading

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