OXFORD

INTERNATIONAL EDITION

Oxford Textbook of Medicine

SIXTH EDITION
VOLUME 3

EDITED BY
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Volume 3: Sections 16–21

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UNIVERSITY PRESS

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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First Edition published in 1983
Second Edition published in 1987
Third Edition published in 1996
Fourth Edition published in 2003
Fifth Edition published in 2010
Sixth Edition published in 2020

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data

Data available

Library of Congress Control Number: 2018933144

Set ISBN: 978–0–19–874669–0
Volume 1: 978–0–19–881533–4
Volume 2: 978–0–19–881535–8
Volume 3: 978–0–19–881537–2
Volume 4: 978–0–19–884741–0

Only available as part of a set

Printed in Malaysia by Vivar Printing

18.9

Bronchiectasis

R. Wilson and D. Bilton

ESSENTIALS

A bronchiectatic lung contains permanently dilated subsegmental airways that are inflamed, tortuous, and often partially or totally obstructed with secretions. Pathogenesis involves airway inflammation which can cause further bacteria-driven host-mediated lung damage. Causes include developmental defects, damage caused by previous infection, immune deficiency, mucociliary clearance defects, and mechanical obstruction, but in many cases (40–60%) the cause is unknown.

Clinical features—bronchiectasis should be suspected when there is a history of persistent cough productive of sputum throughout the year, with chest infections leading to increased symptoms. About 80% of patients have upper respiratory tract symptoms. Clinical examination is often normal, although 'classical' severe cases show finger clubbing and widespread coarse crackles.

Investigation—the 'gold standard' for diagnosis is high-resolution CT of the chest, which reveals dilated bronchi that may be inflamed, causing wall thickening and mucus plugging. The chest radiograph is normal in at least 50% of cases, but abnormal thickened and dilated bronchi may produce tramline opacities and ring shadows. Investigations to determine the underlying cause will be determined by clinical suspicion but should include tests for treatable conditions (e.g. immunoglobulin deficiency, allergic bronchopulmonary aspergillosis, and nontuberculous mycobacteria). Disease status is assessed by high-resolution CT, lung function tests, sputum culture, and measurement of inflammatory markers.

Management—involves the treatment of the specific underlying cause (when possible) and treatment of the bronchiectasis itself, with the most important elements being sputum clearance by physiotherapy and antimicrobials, which need to be given in high dose. Patients with more severe disease, who have frequent exacerbations and are often chronically infected with *Pseudomonas aeruginosa*, may be treated with continuous nebulized antibiotics or oral macrolide antibiotics. Surgery can be a curative for patients with single lobe, focal bronchiectasis, and lobar resection may also be indicated for otherwise uncontrollable bleeding, or if it is felt that a particular lobe is acting as a 'sump' of infection which prevents good control of symptoms with medical therapy. Lung transplantation may be appropriate in carefully selected cases.

Introduction

The definition of bronchiectasis is based on morbid anatomy described first by Laennec as abnormal chronic dilatation of the bronchi. The word itself is from the Greek *bronchion* (windpipe or tube) and *ektasis* (stretched out or extension). In 1819 Laennec described the condition in an infant who died following whooping cough, but by 1891 it was recognized in a textbook of medicine that bronchiectasis was 'not a separate disease' but 'a result of various affectations of the bronchi'. Thus bronchiectasis is not a precise diagnosis but the final pathology of a number of causes which may require their own specific treatment. The 'gold standard' for diagnosis today is the presence of abnormal dilated bronchi on high-resolution CT in a patient with a persistent cough productive of sputum.

Epidemiology

Estimates in the United Kingdom up to 1953 varied from 0.77 to 1.3 per 1000 population, but it seems that following the introduction of antibiotic therapy for pulmonary infection, the control of tuberculosis, and effective vaccination for whooping cough and measles, that the prevalence of bronchiectasis in the United Kingdom—at least of the more severe type—had fallen, as judged by a reduction in hospital admissions and deaths. However, recent studies have suggested that the prevalence is increasing in the last decade in Europe and the United States. For example, a recent study based on healthcare claims in the United States of America suggested an estimated prevalence ranging from 4.2 per 100 000 persons aged 18–34, to 271.8 per 100 000 among those aged 75 years and older. Prevalence was higher in women than men at all ages. The ageing population, use of therapeutic agents that reduce host defence e.g. in rheumatological conditions, CT scans in chronic obstructive pulmonary disease (COPD) showing coexistent bronchiectasis, and an increase in the prevalence of nontuberculous mycobacterial infections may all have led to this increase. However, since the diagnosis of bronchiectasis depends on the cardinal feature of abnormal chronic dilation of one or more bronchi, it is likely that people with chronic sputum production previously not investigated by bronchography or CT may have been mislabelled as 'bronchitic', leading to historical

underestimation of the true prevalence. Only the development of noninvasive imaging applied to large community surveys will tell us the true prevalence of bronchiectasis in the population.

In less developed countries, where antibiotics are less readily available, socioeconomic conditions are poor, and the prevalence of both tuberculosis and HIV infection are high, bronchiectasis is regarded as a common problem.

Pathology

Macroscopic inspection of bronchiectatic lung reveals permanent dilatation of subsegmental airways, which are inflamed, tortuous, and often partially or totally obstructed with secretions. The process also includes bronchioles, and at end stage there may be marked fibrosis of small airways.

In allergic bronchopulmonary aspergillosis (ABPA) the changes are predominantly in proximal airways, and bronchiectasis caused by cystic fibrosis, post-tuberculosis, and ABPA is likely to be more marked in the upper lobes. There is a spectrum of disease ranging from cylindrical, where there is uniform dilatation, to saccular, where there may be gross terminal dilatation of the end bronchi (saccules or cysts). An intermediate form is termed varicose bronchiectasis, when dilatation along the length of the bronchus is uneven.

Microscopic features

The overall appearance is of chronic inflammation in the bronchial wall, with inflammatory cells and mucus in the lumen. Neutrophils are the dominant cell population in the bronchial lumen, with mainly mononuclear cells in the bronchial wall. There is characteristic destruction of the elastin layer of the bronchial wall with a variable amount of fibrosis. The label follicular is applied when, as part of extensive mural inflammation, there is lymphoid follicle formation, which may in subepithelial sites cause finger-like projections blocking the bronchial lumen.

Aetiology and pathogenesis

There is a broad spectrum of causes and underlying conditions associated with bronchiectasis: these are summarized in Table 18.9.1.

Table 18.9.1 Causes of bronchiectasis and associated conditions

Type of cause	Examples
Developmental defects	Structural Deficiency of bronchial wall (e.g. Williams–Campbell syndrome and Ehlers-Danlos syndrome)
	Pulmonary sequestration
	Tracheobronchomegaly (Mounier–Kuhn syndrome)
Immune deficiency	Primary:
	Panhypogammaglobulinaemia
	Selective immunoglobulin deficiency
	Secondary:
	HIV infection
	Malignancy (chronic lymphocytic leukaemia)
Excessive immune response	Allergic bronchopulmonary aspergillosis
	Post lung transplantation α-1 antitrypsin deficiency
Mucociliary clearance defects	Primary ciliary dyskinesia
	Cystic fibrosis
	Young's syndrome
Toxic insult	Aspiration of gastric contents
	Inhalation of toxic gases or chemicals (e.g. ammonia)
Mechanical obstruction	Intrinsic (e.g. tumour or foreign body)
	Extrinsic (e.g. tubercular lymph node)
Post-infective	*Bordetella pertussis*
	Measles
	Tuberculosis Nontuberculous mycobacteria
Associated conditions	Chronic rhinosinusitis
	Rheumatoid arthritis
	Inflammatory bowel disease (ulcerative colitis, Crohn's disease)
	Coeliac disease
	Yellow nail syndrome
	Connective tissue disorders and vasculitides
Idiopathic	

The pathogenesis of bronchiectasis requires the combination of an infectious insult with associated impaired clearance mechanisms that may result from structural abnormalities of the airway, impaired mucociliary clearance, or defective immune defences. Experimental animal models support the theory that local obstruction and infection distal to the obstruction are both required in order to produce bronchiectasis. Furthermore the infection is required to be active, with damage to the airway wall then occurring as a result of direct microbial insult and the secondary effects of the host inflammatory response which is driven by the bacterial infection. It has been proposed that a 'vicious cycle' explains the development of bronchiectasis in a predisposed individual given a trigger insult (Fig. 18.9.1). Neutrophil elastase is thought to play a key role. Neutrophils are recruited as part of the natural defences, but the inflammation is not self-limiting and in patients with bronchiectasis neutrophils traffic into the airway lumen, attracted by persistent bacterial infection, with free neutrophil elastase activity usually present. Elastase, a neutrophil-derived serine proteinase, is known to digest elastin, which is an important structural protein of the bronchial wall, inhibit ciliary beating, damage epithelia, act as a mucus secretagogue, and inhibit opsonophagocytosis via cleavage of immunoglobulins. All these actions contribute to persistence of bacteria in the respiratory tract and to long-term tissue damage.

Fig. 18.9.1 clearly demonstrates that however a patient enters the pathway (e.g. following damage to the airway by an infectious insult such as tuberculosis, or primary ciliary dyskinesia which inhibits mucociliary clearance, or with immunoglobulin deficiency which favours persistence of microbes in the bronchial tree), the vicious cycle becomes self-perpetuating with the final outcome of airway damage, which might spread into the normal bystander lung.

Developmental defects

The congenital forms of bronchiectasis frequently show deficiency of the elements of bronchial wall which are necessary to

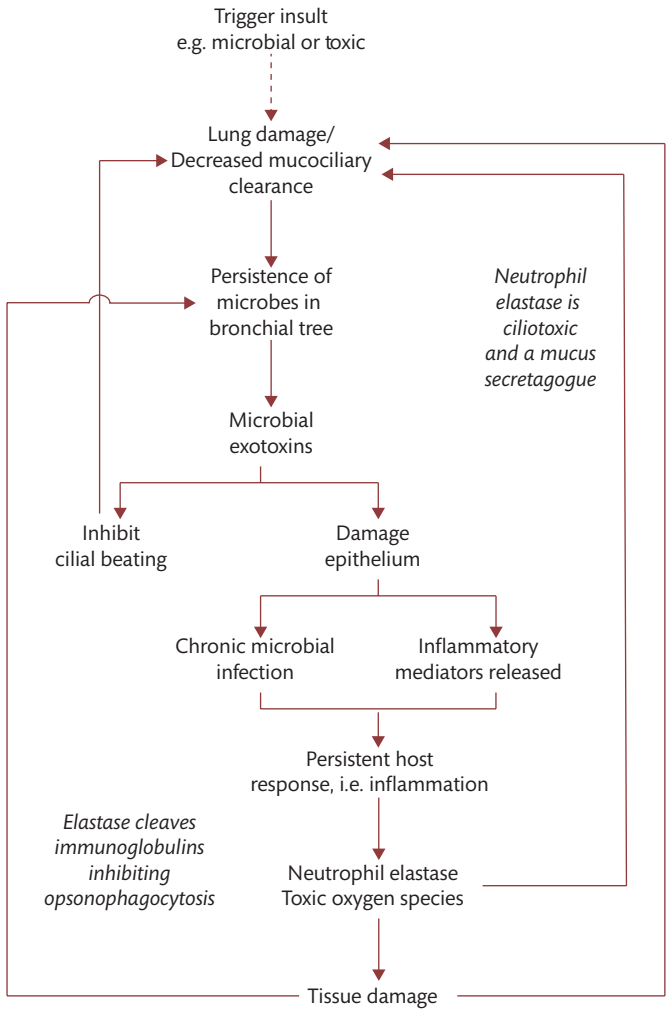

Fig. 18.9.1 The vicious cycle of infection and inflammation leading to progressive tissue damage in bronchiectasis.

maintain normal anatomy and prevent collapse, and hence 'obstruction' of the airway. They may occur due to premature degeneration as well as congenital absence/abnormality. Mounier–Kuhn syndrome describes tracheobronchomegaly, which as the name suggests describes severe proximal dilatation, while Williams–Campbell syndrome occurs due to deficiency of bronchial cartilage. Pulmonary sequestration predisposes to bronchiectasis because of repeated infections in the affected segment caused by poor clearance.

Immune deficiency

Childhood bronchiectasis should trigger an extensive assessment of phagocytic and cellular immune defences. X-linked hypogammaglobulinaemia, a rare disorder, presents early in life, with bronchiectasis a frequent complication if untreated. Adult-onset common variable immunodeficiency or panhypogammaglobulinaemia frequently presents with recurrent respiratory infection and is complicated by bronchiectasis if untreated. Selective immunoglobulin deficiencies of a particular class and functional antibody deficiencies (e.g. failure to respond in the normal way to polysaccharide antigen), also occur. The importance of functional antibody deficiencies in the presence of normal immunoglobulin levels has been recognized as a risk factor for recurrent respiratory tract infections and development of bronchiectasis. In subjects with low levels of specific antibodies to polysaccharide antigen (e.g. *Streptococcus pneumoniae* or *Haemophilus influenzae* type b), the patient should be vaccinated and the levels measured again after 6 weeks. Failure to mount and maintain adequate responses to the vaccination is a milder form of common variable immunodeficiency. Patients with functional antibody deficiency and normal immunoglobulin levels can be managed with prompt antibiotic therapy but may require immunoglobulin therapy if there is evidence of disease progression despite optimal antibiotic treatment.

Immune defects may be secondary to malignancy or be related to treatment with immunosuppressive agents. In addition, bronchiectasis is now a recognized complication of HIV disease.

Excessive immune response

Fig. 18.9.1 illustrates the damage that may occur as a result of the host response to chronic airway infection. ABPA is a condition in which excessive eosinophilic inflammation caused by the bodies reaction to inhaled fungal spores characteristically causes proximal upper-lobe bronchiectasis. The appearance of obliterative bronchiolitis and subsequent bronchiectasis in lung transplant rejection further highlights the role of a damaging immune response in the development of the condition. α-1 antitrypsin deficiency more commonly causes emphysema due to unopposed neutrophil elastase, particularly in patients who smoke, but in some patients bronchiectasis is the predominant disease for reasons which are not understood.

Disorders of mucociliary clearance

Cystic fibrosis provides the archetypal model of a genetic predisposition for the development of bronchiectasis. In this disorder there is dysfunction of the cystic fibrosis transmembrane regulator (CFTR), a transmembrane chloride channel and ion transport regulatory protein. The resulting abnormal salt and water transport across respiratory epithelia predisposes to respiratory infection and the effects of the vicious cycle are clearly demonstrated as a structurally normal lung suffers progressive airway damage and the development of bronchiectasis.

In primary ciliary dyskinesia ineffective ciliary beating impairs mucociliary clearance, leading to mucus retention and recurrent infections in the paranasal sinuses, middle ear, and lungs, with progression to bronchiectasis. It is an inherited disorder, mostly in an autosomal recessive pattern, with an estimated incidence of 1 in 15 000 to 1 in 30 000 births. The diagnosis is made by light microscopy to examine ciliary beat pattern and electron microscopy to examine ultrastructure. Nasal nitric oxide concentrations are extremely low in primary ciliary dyskinesia and provide a useful screening test to identify patients for further investigation with brush biopsy of the nasal epithelium. In the largest subgroup of this syndrome, in which electron microscopic appearances were originally described, the cilia were found to lack dynein arms, the structure responsible for movement of cilia or spermatozoa. Subsequently it has been appreciated that a range of components of the cilia are affected. Much progress has been made in recent years identifying the genetic defects responsible for the ultrastructural abnormalities, and in explaining primary ciliary dyskinesia with normal ultrastructure. The gene that encodes the

human intermediate dynein, *DNAI1*, has been shown to exhibit recessively inherited mutations in some primary ciliary dyskinesia families. Furthermore, mutations in *DNAH5*, the gene encoding a heavy chain of the outer dynein arm, have been shown in almost one-half of primary ciliary dyskinesia subjects that have defects of this dynein arm.

The intriguing observation that about 50% of all subjects with immotile cilia syndrome have situs inversus is true for most subgroups, apart from those who have absent cilia or those whose main characteristic is lack of the two central microtubules. When ciliary dyskinesia is associated with abnormal situs the condition is called Kartagener's syndrome after the paediatrician who described four patients with the association of dextrocardia, sinusitis, and bronchiectasis in 1933.

Young's syndrome seems to represent an acquired defect of mucociliary clearance in which obstructive azoospermia is associated with sinusitis and bronchiectasis. The condition may occur after successful parentage and may be associated with mercury poisoning from 'tooth powders' used in infancy (Pink's disease). Secondary ciliary dyskinesia refers to the situation in which cilia are intrinsically normal but ciliary beating is reduced because of toxic damage from neutrophil or bacterial products. Tobacco smoke and other environmental pollutants have also been implicated in reducing ciliary beat frequency.

Toxic insult

In some patients (e.g. fire victims) there is a clear history of an inhalation accident or exposure to hot gases. Aspiration of gastric contents is another important cause of bronchiectasis, in that treatment to prevent aspiration will prevent further airway damage.

Mechanical obstruction

Bronchiectasis confined to a single lobe may be the result of a local mechanical obstruction either in the lumen (intrinsic), for example, tumour or foreign body, or originating outside the lumen (extrinsic), for example, from lymph node enlargement from tuberculosis or tumour (Fig. 18.9.2). In patients with localized bronchiectasis, a bronchoscopy should be considered to exclude an obstructing lesion.

Post-infective bronchiectasis

The true incidence of post-infective bronchiectasis is difficult to confirm, as studies are retrospective, relying on memory or histories obtained 'second hand' from parents. The microorganisms known to cause infection likely to progress to bronchiectasis are *Bordetella pertussis*, measles virus, adenoviruses, *Trypanosoma cruzi, Mycobacterium tuberculosis,* and nontuberculous mycobacterial infections, which have become more prevalent in recent years. These can cause primary infections that lead to bronchiectasis, or can infect patients with bronchiectasis from another cause. *Mycobacterium avium complex* and *M. abscessus* are the two species most often implicated.

Some patients who present with symptoms of bronchiectasis in adult life may report a childhood episode of whooping cough or measles, but it is uncertain how relevant this history is to their presentation if there has been a prolonged period without symptoms, and patients should only be labelled as post-infective if symptoms have been persistent, without remission since childhood.

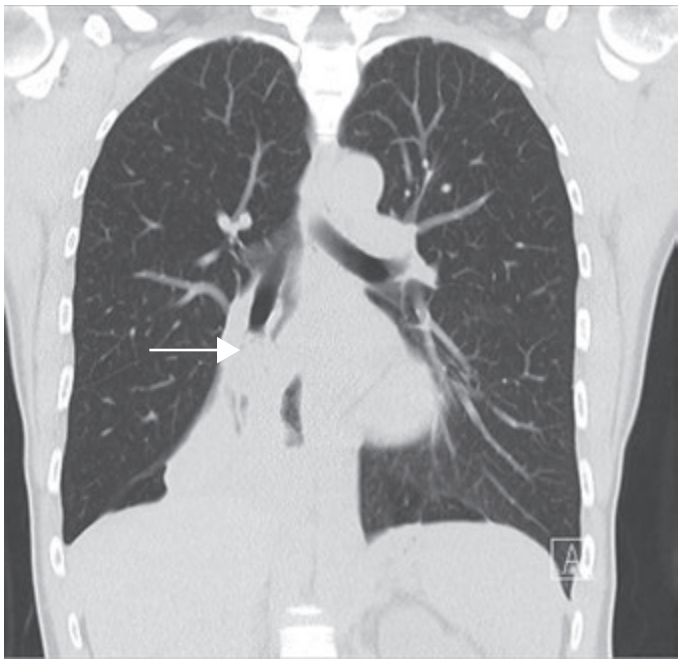

Fig. 18.9.2 Carcinoid tumour in the intermediate bronchus (see arrow). The patient presented with localized bronchiectasis in the right lower lobe.

Associated conditions

The association of rheumatoid arthritis with bronchiectasis is well recognized. Patients often have marked small airways disease. Treatment needs to achieve the right balance of immunosuppression, which helps the underlying inflammatory disease process, but may impair antimicrobial defences. The association between inflammatory bowel disease, most commonly ulcerative colitis, and bronchiectasis highlights the usefulness of immunosuppression, as some patients with both conditions report an improvement in chest symptoms when they take systemic corticosteroids. The classic presentation is that a patient without any respiratory history presents several months after pan-colectomy for ulcerative colitis with a productive cough. Patients will often produce large volumes of purulent sputum which is sterile, and the CT scan shows diffuse inflammatory changes which can progress to bronchiectasis.

Idiopathic

Even in specialist bronchiectasis clinics, the underlying cause of bronchiectasis remains unknown in 40–60% of patients, who are currently labelled as having 'idiopathic' disease. The most common presentation is with onset of productive cough in adult life, symmetrical predominantly lower lobe cylindrical bronchiectasis, and chronic rhinosinusitis.

Clinical features

History

Bronchiectasis should be suspected when there is a history of persistent productive cough throughout the year. Patients have often been treated for recurrent chest infections and labelled as 'bronchitic', sometimes despite the absence of a smoking history.

Early in the disease patients may produce mucoid sputum until they suffer an exacerbation associated with viral upper respiratory tract infection, when the sputum becomes purulent due to secondary bacterial infection. Exacerbations involve increased sputum volume and purulence, breathlessness, and may be associated with pleuritic chest pain, haemoptysis, and fever, and patients may also become wheezy.

About 80% of patients with bronchiectasis have upper respiratory tract symptoms, with postnasal drip being the most common. About 30% have chronic sinus infection, with fewer having recurrent ear infections, although the latter are often present in primary ciliary dyskinesia. Patients with bronchiectasis also suffer from undue tiredness, which many find just as troublesome as the productive cough.

Examination

'Classical' severe cases of bronchiectasis seen in the preantibiotic era or in less developed countries are associated with obvious clinical signs including finger clubbing and widespread coarse crackles. Nowadays it is much more likely for clinical examination to be normal: the absence of clubbing or lung crackles does not exclude bronchiectasis.

Pulmonary function tests usually show airflow obstruction, but mild restriction is also recognized, particularly in patients with loss of volume in the affected lobes.

Investigation and diagnosis

Radiological imaging

The gold standard for the diagnosis of bronchiectasis is thin-section high-resolution CT of the chest, which has replaced the more invasive investigation of bronchography. Dilatation is present if the internal diameter of the bronchus is greater than the diameter of its accompanying pulmonary artery. The classic appearance of a cross-section of a thick-walled dilated bronchus next to the accompanying pulmonary artery is the 'signet ring', as shown in Fig. 18.9.3. Bronchial dilatation is also recognized when airways are seen in longitudinal section on CT and there is a failure of tapering as the bronchus courses towards the periphery.

There is a morphological spectrum of bronchiectasis, with cylindrical bronchiectasis forming one group, cystic or saccular bronchiectasis at the other end of the spectrum, and an intermediate group termed varicose bronchiectasis also recognized. The CT appearances are well described: in cylindrical bronchiectasis there is uniform dilatation of the bronchi as they extend towards the periphery; cystic bronchiectasis is recognized by rings representing the markedly dilated bronchi, which may be clustered together and may contain air fluid levels; varicose bronchiectasis produces a beaded appearance, best shown when bronchi are imaged in the plane of the scan. Active inflammation is illustrated by airway wall thickening, mucus plugging of small ('tree-in-bud' appearance of exudative bronchiolitis) and large airways, and patches of consolidation.

The chest radiograph is normal in at least 50% of patients with CT or bronchographic evidence of bronchiectasis. If the chest radiograph is abnormal, the findings relate to abnormal thickened and dilated bronchi which produce tramline opacities and ring shadows.

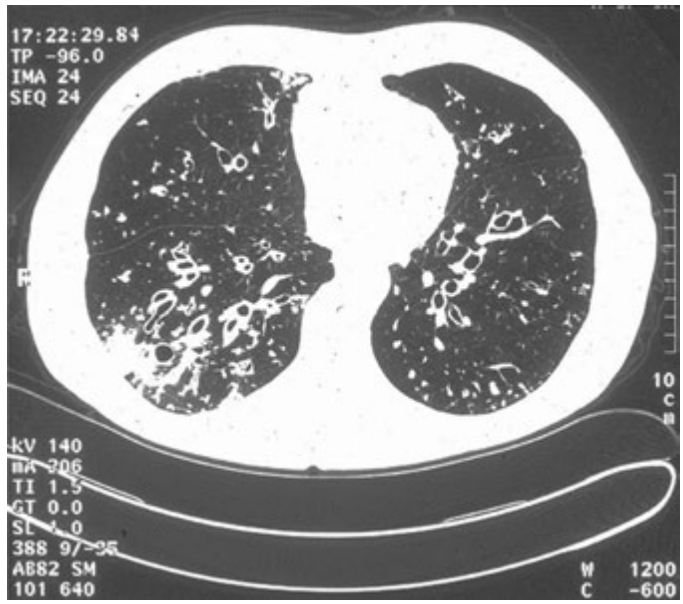

Fig. 18.9.3 A CT scan of a patient with bronchiectasis showing many characteristic 'signet ring' signs.

Retained mucus may be manifest as tubular opacities, and there may be associated volume loss of the affected lobe.

Determining the state of disease

Once high-resolution CT has proven the presence of bronchiectasis, investigations are directed at defining the current status of the disease and then at attempting to define an underlying cause. Table 18.9.2 highlights the minimum required to assess the current disease status.

Examination of a sputum specimen is crucial, it being important to document the character of the sputum (i.e. mucoid or purulent) and to determine the infecting organism. The common bacteria are nontypeable *Haemophilus influenzae, Moraxella catarrhalis, Streptococcus pneumoniae*, and *Pseudomonas aeruginosa. H. influenzae* is the most common (40–60%). *P. aeruginosa* is usually associated with worsening symptoms and more severe lung disease. As patient's sputum microbiology may alter over time it is helpful to obtain repeated samples to ensure that an appropriate antibiotic management plan is in place.

Measurement of inflammatory markers allows an assessment of the patient's current 'inflammatory burden'. Patients may come

Table 18.9.2 Investigations to assess current disease status

Investigation	Purpose
High-resolution CT	Assess extent of bronchiectasis
Lung function tests	To assess airflow obstruction, lung volumes, and gas trapping Include assessment of reversibility to β2 agonists and anticholinergic agents
Sputum culture	To assess infecting microorganisms, including culture for acid-fast bacilli and fungi
Haematology	Differential white count, ESR, and CRP

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate.

Table 18.9.3 Investigations to assess underlying causes of bronchiectasis

Investigation	Purpose
Bronchoscopy	If CT suggests bronchial obstruction—to establish whether tumour or foreign body is present
Nasal brushing/biopsy	To establish ciliary beat frequency, beat pattern, and obtain tissue for EM of cilia
Nasal nitric oxide	Screening test for primary ciliary dyskinesia
Semen analysis	If primary ciliary dyskinesia, Young's syndrome, or CF is suspected
CF genetics and sweat test	To exclude CF
Immunoglobulins and vaccine responses to Pneumovax, Hib, and tetanus	To identify immunodeficiency
Barium swallow, videofluoroscopy ± oesophageal manometry	If aspiration is suspected
α1-Antitrypsin measurement	To identify α1-antitrypsin deficiency
Autoantibody screen	To identify associated connective tissue disorders or vasculitis
Aspergillus skin testing and IgE and RAST to aspergillus	To identify ABPA

ABPA, allergic bronchopulmonary aspergillosis; CF, cystic fibrosis; EM, electron microscopy, Hib, *Haemophilus influenzae* B; RAST, radioallergosorbent test.

to accept persistent purulent sputum over a period of time and not complain of being particularly unwell, in which case a raised erythrocyte sedimentation rate and/or C-reactive protein would weigh the argument in favour of early antibiotic intervention.

Determining the cause of disease

Table 18.9.3 outlines the investigations required to investigate a cause of bronchiectasis, and it is important to emphasize that knowledge of the aetiology of bronchiectasis does alter management and thus prognosis. Panhypogammaglobulinaemic patients are transformed by immunoglobulin replacement; ABPA is a treatable cause of bronchiectasis, with corticosteroid treatment and/or antifungal antibiotics producing major improvements in symptoms and well-being, restoring lung function, and preventing the development of further bronchiectasis; untreated *M. avium complex* infection may progress inexorably; rheumatoid arthritis, inflammatory bowel disease, primary ciliary dyskinesia, and cystic fibrosis (CF) all have different treatments specifc to their diagnosis. Similarly, the appreciation that chronic aspiration is the precipitant of lung damage leads to appropriate therapeutic manoeuvres aimed at prevention of further damage.

Cystic fibrosis/bronchiectasis overlap

The diagnosis of CF should be considered in any patient with unexplained bronchiectasis (particularly of the upper lobes) beginning in childhood. Mixed infection with S*taphylococcus aureus* and *P. aeruginosa* should also raise the possibility. Male infertility and a family history are useful pointers when present, but a normal sweat test does not exclude the diagnosis, in particular in mutations which produce mild disease. The diagnostic label of atypical cystic fibrosis has been coined to describe patients with mild nonclassic cystic fibrosis: where there is diagnostic doubt, the patient should be referred to a specialist cystic fibrosis centre for further investigations.

Management

The principles of management of bronchiectasis are outlined in Box 18.9.1. The medical approach is two-pronged, with close attention given to treating any underlying cause while also treating the established bronchiectasis.

Box 18.9.1 Principles of management of bronchiectasis

- Medical treatment specific to the determined cause of bronchiectasis (if present)
- Medical treatment for bronchiectasis:
  - Sputum clearance
  - Physiotherapy
  - Mucolytic therapy
  - Antimicrobial therapy for acute exacerbation
  - Continuous antibiotic prophylactic therapy
  - Anti-inflammatory therapy
  - Bronchodilator therapy
- Surgical treatment:
  - Resection of localized bronchiectasis; resection of severe disease acting as a 'sump' leaving milder disease elsewhere
  - Lung transplantation for end-stage disease

Sputum clearance

As mucociliary clearance is reduced in bronchiectasis, and excess secretions that build up contain bacteria and inflammatory mediators, it seems sensible to assist sputum clearance. This can be achieved in several ways including physical exercise; physiotherapy breathing techniques which may incorporate percussion and postural drainage (Table 18.9.4); and various assist devices that can be used to assist expectoration. This does not simply prevent mucus retention but also allows a patient to expectorate sputum at a chosen convenient time, rather than coughing throughout the day or night. There are insufficient controlled trials to prove or disprove their usefulness in terms of disease modification or survival.

The use of mucolytics in bronchiectasis is controversial. The success of DNase in CF has not been repeated in bronchiectasis with another cause. There is limited evidence to support the use of nebulized hypertonic saline, but patients with sticky secretions report this helpful. A study of inhalation of an osmotic agent, dry powdered mannitol, failed its primary end point of reducing exacerbations but did improve patients' sense of well-being. Some

Table 18.9.4 The active cycle of breathing technique to help expectorate sputum

1) 3 or 4 quiet breaths to relax 'breathing control'
2) 3 or 4 slow deep breaths in and out 'deep breaths'
Huffing
3) Take a medium sized breath in
4) Squeeze the breath out by contracting the abdominal muscles keeping mouth and throat open. The breath should be prolonged, but not continued until the lungs are empty
5) Take a large breath in
6) Squeeze the air out as before
7) Cough and expectorate any sputum. If you don't produce any sputum with 1 or 2 coughs, try to stop coughing by using your breathing control
8) Allow your breathing to settle with breathing control and then repeat the cycle until your chest feels clear

patients also report sputum easier to expectorate when taking an oral mucolytic (e.g. carbocisteine).

Antimicrobial therapy

The modern approach to antimicrobial treatment in bronchiectasis has been derived from regimens used in CF that have yielded impressive results in survival. There are three approaches to the use of antimicrobial therapy in bronchiectasis. The first involves the treatment of acute exacerbations. The second is based on the 'vicious cycle' hypothesis, suggesting that continuous (inhaled or oral) targeted antimicrobial therapy reduces bacterial numbers, thereby reducing the level of inflammation and hence improving patient well-being and reducing the potential for further lung damage. Recent clinical trials have shown that inhaled antibiotics cause a marked reduction in bacterial numbers in sputum, which may decrease symptoms. There is limited evidence that this is translated into decreased exacerbations, but this has been shown in two studies, one with gentamicin and the other colomycin, and several other trials are ongoing. The third approach is long-term oral macrolide therapy, which has been shown in several studies to reduce exacerbation frequency and might benefit patients by a combination of the antibacterial and anti-inflammatory properties of this class of antibiotic.

Developing an antibiotic regime for treatment of bronchiectasis depends on knowledge of a patient's infecting organism, but several principles apply regardless of the bacterial species. First, high doses are often required to penetrate scarred, thickened bronchial walls, and the tenacious secretions act as a physical barrier to reduce antibiotic penetration to the microbes while harbouring drug-inactivating enzymes such as β-lactamases. Secondly, to avoid a high oral dose of an antibiotic, which may result in unacceptable side effects, the nebulized or parenteral route is often employed to achieve high levels of drug in the bronchial lumen. Thirdly, a longer course of antibiotic is often required (e.g. 14 days). Finally, to determine the best treatment regimen for a patient, it is worth assessing their initial response to an agent appropriate for the infecting organism, in particular the rapidity of return of purulent sputum. If purulent sputum becomes mucoid after a 14-day course of oral antibiotics and remains mucoid until the next viral trigger, then one is likely to recommend 'exacerbation only' treatment. By contrast, if sputum returns to being purulent within a few days of treatment finishing, it is likely that continuous suppressive therapy will be required.

Patients with chronic *Pseudomonas aeruginosa* infection usually have more severe disease and worse airflow obstruction, and because of this they suffer increased morbidity and mortality. Although they may respond to oral ciprofloxacin initially, resistance often develops with repeated courses, and it is much more likely that an acute exacerbation will require intravenous antibiotic therapy with appropriate anti-pseudomonal antibiotics. Furthermore, these patients will often require maintenance therapy with nebulized antibiotic and/or an oral macrolide antibiotic to control symptoms and prevent exacerbations.

Fig. 18.9.4 suggests a plan for developing a regimen for a patient depending on the characteristics of their sputum and the infecting organism.

Inhaled antibiotics

This mode of treatment has the advantage of achieving high concentrations of antibiotic in the airway lumen, which improves bacterial killing and makes resistance development less likely. There are several antibiotics in development for inhaled therapy, but at the moment the choice lies between colomycin and gentamicin, since tobramycin and aztreonam have a licence in CF only. A recent meta-analysis included eight trials with 590 patients in which nebulized aminoglycosides, ciprofloxacin, aztreonam, or colomycin were given for 4 weeks to 12 months compared to placebo. These were more effective than placebo in reducing sputum bacterial load, eradicating bacteria from sputum, and most importantly reducing the risk of exacerbations. Ten per cent (10%) of patients experienced bronchospasm after taking the inhaled antibiotic, so a supervised trial with spirometry before and after should be conducted.

Bronchodilator therapy

Patients with bronchiectasis may have a restrictive or an obstructive picture. Some patients will have significant reversibility, hence it is worth assessing each individual for their response to β2-agonists and anticholinergic agents.

Anti-inflammatory therapy

The 'vicious cycle' hypothesis suggests that the addition of anti-inflammatory therapy to antibiotics should be of benefit. Trials of oral corticosteroids have shown significant benefit in terms of lung function in cystic fibrosis. Short-term trials of inhaled corticosteroids have been carried out in bronchiectasis, but the evidence for their use is limited and further trials are required. A trial of inhaled steroids is justified if the patient has significant airflow obstruction, particularly if they have benefited from oral steroids, but objective measures should be taken and the inhaled steroids stopped if no improvement is demonstrated. However, benefits may be seen in symptoms other than airflow obstruction, such as cough frequency, sputum volume, and ease of expectoration, so the assessment may not be straightforward.

Therapy with macrolides

Macrolide antibiotics were first shown in Japan to benefit patients with diffuse panbronchiolitis, an inflammatory airway condition

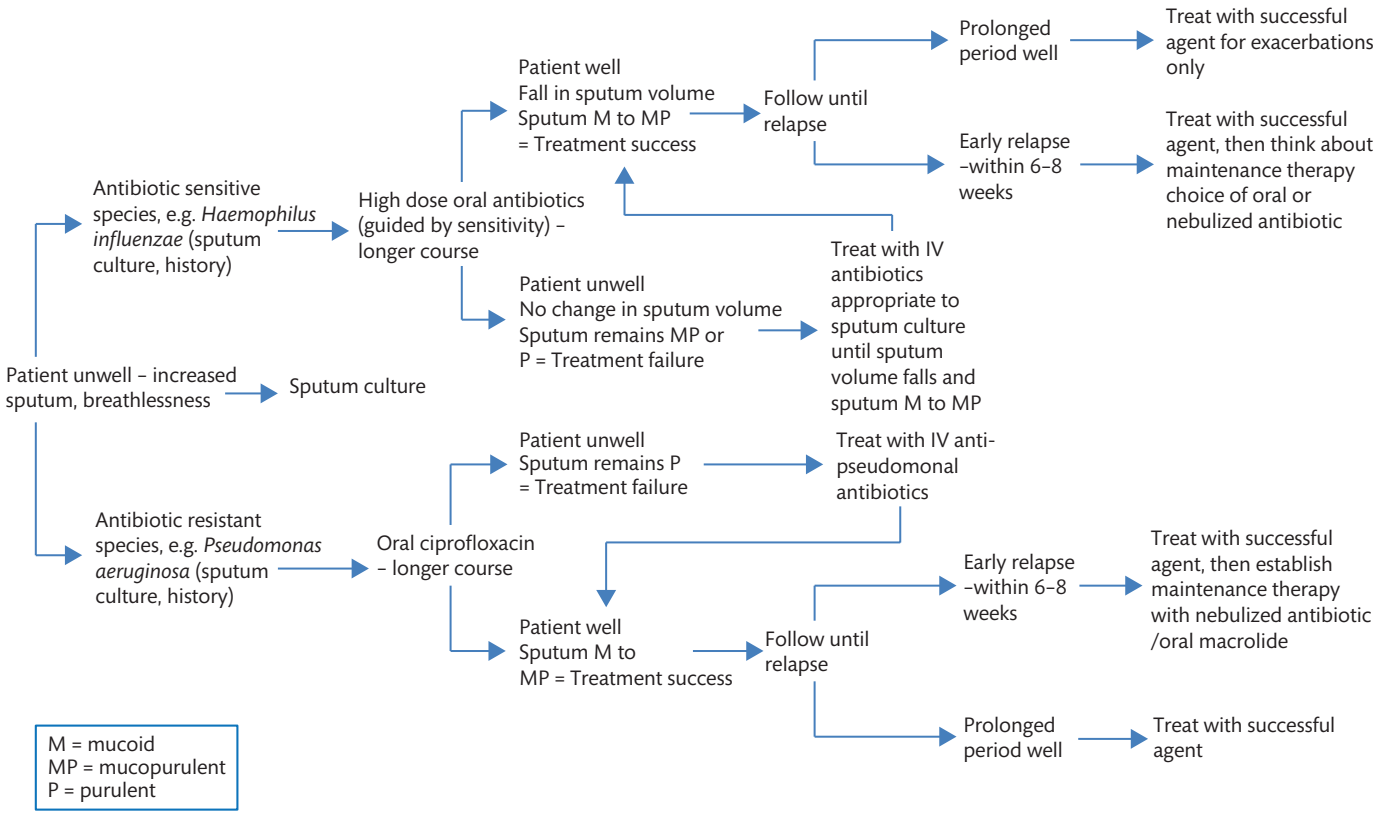

Fig. 18.9.4 Guide to therapy for patients with bronchiectasis.

which can progress to bronchiectasis. Three double-blind placebo controlled trials have shown their benefit in bronchiectasis in terms of reducing exacerbation frequency, improving lung function, reducing sputum volume, and improving quality of life. Several meta-analyses of published trials have confirmed these benefits. The mechanism of action is thought to be immunomodulation, but macrolides build up to very high concentrations within phagocytes and a direct effect on bacteria may occur, which might be bacterial killing, suppression of bacterial growth, or inhibition of production of bacterial virulence factors. Azithromycin is the macrolide most often chosen. Different treatment regimens have been used in the trials, but 250 mg or 500 mg (chosen depending on severity of disease and patient size) three times weekly (Monday, Wednesday, and Friday) is commonly adopted. This is well tolerated and makes use of the pharmacokinetics of the antibiotic which concentrates and persists in tissues.

Gastrointestinal disturbance and hearing impairment are the most common side effects of long-term macrolide treatment. Patients must be warned before starting treatment that if tinnitus or impaired hearing occurs, they must stop the antibiotic and seek advice. Full blood count, renal and liver function should be monitored about every 3 months.

Macrolides are an important part of the treatment of non-tuberculous mycobacteria, and patients should have a negative sputum for acid-fast bacilli before starting treatment to avoid the development of macrolide resistance. Concern has also been expressed from a societal viewpoint about increase in macrolide resistance with widespread long-term use.

Monitoring response to treatment

Each patient should have a tailored management plan, which should include instructions about physiotherapy, antibiotic prophylaxis if used, and antibiotic management during an infection. It is critical that both the patient and physician agree defined criteria for assessing response. Lung function produces an objective measure of response, but the introduction of antibiotics may not alter lung function to a great degree, although it should improve sputum colour, volume, and consistency, and reduce exacerbation frequency. This leads to an improvement in general well-being. Diary cards documenting these parameters have proved helpful, and studies have confirmed the validity of grading sputum colour as a marker of the microbial and inflammatory load in these patients. A number of disease-specific health status questionnaires have been developed and these may be used in the future. This approach also facilitates patient education and self-management plans.

Surgery

Surgery is the only 'curative' treatment for a select group of patients and should be carefully considered. In particular, for single-lobe, focal bronchiectasis, surgery removes the need for lifelong medical therapy. However, it is important that patients undergo careful assessment regarding the distribution of bronchiectasis and the possibility of underlying causes which would predispose to disease recurrence. Surgery is unlikely to produce a cure if bronchiectasis is present in several lobes, and lobar resection is then indicated only if there is uncontrolled bleeding unresponsive to bronchial artery embolization, or if it is felt—after a failure of aggressive antimicrobial

therapy—that a particular lobe is acting as a 'sump' of infection which prevents good control of symptoms with medical therapy.

Lung transplantation

Lung transplantation provides an effective treatment for end-stage bronchiectasis, providing that an underlying cause has been carefully assessed and treated and is unlikely to jeopardize the transplanted organs (e.g. patients with immunoglobulin deficiencies are not discounted from transplant assessment provided they are receiving adequate immunoglobulin replacement therapy).

Complications

The most common complication to precipitate hospital admission in patients with bronchiectasis is infective exacerbation, which may be associated with pleuritic chest pain and minor haemoptysis. Massive haemoptysis is rare nowadays, but is managed by bronchial artery embolization. Metastatic spread of infection rarely occurs in the developed world with good control of pulmonary infection with antibiotics, and for similar reasons empyema is now very rare. Amyloidosis is described as a 'classic' complication of bronchiectasis, but is now extremely rare in the United Kingdom. Arthropathy is a complication of bronchiectasis which seems to flare in association with the chest disease, and antimicrobial treatment will often result in remission of joint pain. Some patients may suffer vasculitic skin lesions in association with flares of bronchiectasis.

Prognosis

It was reported in 1940 that 70% of 400 patients with bronchiectasis were dead before the age of 40. The situation is clearly different now, as in the developed world we do not often see the florid post-infective saccular type of bronchiectasis, but more commonly see patients presenting in their fourth and fifth decade of life with CT findings of cylindrical bronchiectasis. However, bronchiectasis does shorten life as well as impacting on patient well-being. One study of 116 patients identified a 14-year survival of 81%, while another of 372 patients an 8.8 year survival of 75%, and another of 91 patients followed prospectively for 13 years showed 70.3% survival. On multivariate analysis, poor exercise capacity, *Pseudomonas* infection, and lung function impairment (obstruction with restriction) were identified as independent factors associated with mortality. In a subsequent CT scan analysis of the same patients, pulmonary hypertension was identified as the most important radiological feature associated with mortality.

A Finnish study published in 1997 used the national hospital discharge register to identify patients with newly diagnosed bronchiectasis from 1982 to 1986, comparing them with age- and sex-matched patients with COPD and asthma discharged at the same time. Over a 10-year follow-up the prognosis for those with bronchiectasis was better than that for patients with COPD, but poorer than that of those with asthma. Bronchiectasis was the main cause of death in 13% of patients with the condition. It is clear in the published studies that chronic *Pseudomonas aeruginosa* infection is associated with increased mortality.

Generally, bronchiectasis progresses slowly, but some patient groups have a worse prognosis. Two prognostic scoring systems have recently been published (the BSI and FACED scores) from studies of patients over a relatively short time period (5 years or less). They have identified similar prognostic factors: age, body mass index, FEV_1, previous hospital admissions, severity of breathlessness, chronic *Pseudomonas* infection, chronic infection by other bacteria, and radiological severity are weighted when calculating the BSI score, whereas the FACED score is simpler and only involves five of these factors.

Future developments

It is likely that a careful search for genetic factors which affect lung defences will yield new causes of bronchiectasis and allow the current so called 'idiopathic' group to be assigned a cause.

The role of inhaled and macrolide antibiotics in bronchiectasis patients with frequent exacerbations needs to be studied further in terms of patient selection for these treatments, the choice of antibiotic and optimal regimen, and their benefits and side effects. Exacerbation frequency or time to first exacerbation after the introduction of the treatment may be blunt tools to assess the benefit of new treatments and will need to be refined. Diary cards to assess number of days with symptoms above a certain level have been used successfully in COPD, and new disease specific quality of life questionnaires may help. However, new biomarkers will be important, and lung clearance index is one such measure recently reported.

The principle of enhancing sputum clearance to break the vicious cycle of infection and inflammation will be investigated further, as will new anti-inflammatory treatments. An approach which reduces exacerbations without recourse to chronic antibiotic therapy will be welcomed.

Finally, given clear evidence of increased mortality associated with chronic *Pseudomonas* infection, the benefits of preventative strategies together with microbiological surveillance and early eradication treatment with antibiotics will need to be explored. Application of molecular techniques that are much more sensitive than sputum culture to identify bacteria soon after they colonize will likely help in this regard.

FURTHER READING

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