James Chalmers
Eva Polverino
Stefano Aliberti *Editors*

Bronchiectasis

The EMBARC Manual

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The European Bronchiectasis Registry

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Preface

> In the long history of humankind (and animal kind, too) those who learned to collaborate and improvise most effectively have prevailed.—Charles Darwin

The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) was formed in 2012 to stimulate clinical and scientific advances in the field of bronchiectasis. The group, representing dedicated clinicians in more than 30 countries, was then established by the European Respiratory Society, the world's largest organisation for respiratory professionals, as a clinical research collaboration initiative (www.bronchiectasis.eu).

In the 5 years since it was formed, EMBARC has made an important contribution to raising the profile of bronchiectasis within the respiratory community. We have established a European Bronchiectasis Registry, the first international initiative of its kind which is on course to enrol 10,000 patients by 2020. EMBARC has published more than 20 papers in 3 years and is actively supporting and initiating both observational and randomised clinical trials. Neglected diseases like bronchiectasis are chronically under-resourced and frequently ignored by the pharmaceutical industry, the media and large-scale academic funders. Only sustained collaboration and formation of supportive networks like EMBARC can achieve the sustained improvements in bronchiectasis care and research that are urgently needed.

The accomplishment of EMBARC represents the shared achievements of a European and more broadly an international coalition of enthusiastic and dedicated doctors, nurses, other healthcare professionals and patients who together give up their time and energy to try to make a difference to a long-neglected disease.

The first 5 years have been the beginning of a journey that we hope ultimately leads to better care for patients, better guidelines, better research and ultimately an end to the suffering of bronchiectasis patients worldwide.

> Science, my boy, is made up of mistakes, but they are mistakes which it is useful to make, because they lead little by little to the truth.—Jules Verne, Journey to the Center of the Earth

Bronchiectasis is many things—a word derived from Greek (bronckos = airway and ektasis = widening); a radiological or pathological appearance, in the present usually seen on computed tomography showing airway dilatation; a disease in which patients experience cough, sputum and frequent chest infections; and a

manifestation of many other diseases which may be genetic (e.g. cystic fibrosis, primary ciliary dyskinesia), developmental (Williams-Campbell syndrome), infectious, autoimmune, toxic, allergic or immunological.

It is also a disease about which the medical professional has been consistently wrong over the course of a century. With the decline in tuberculosis, we were told bronchiectasis would virtually disappear in Western countries. Instead, the disease has increased rapidly. We were told that bronchiectasis was rare—an "orphan disease"—and now, prevalence estimates suggest it is more than 10 times more common than the European threshold for an orphan disease (5 per 10,000 population). Many argued that bronchiectasis is not truly a disease, but rather a manifestation of chronic obstructive pulmonary disease. It has been said to be too heterogeneous to ever be studied or to support evidence-based guidelines. European guidelines for bronchiectasis, a defined and clearly characterised disease, will be published by the European Respiratory Society in 2017. We have spent decades talking about bacterial "colonisation", believing that organisms such as *Haemophilus influenzae* were relatively harmless bystanders only to discover progressively that bacteria are the primary driver of lung inflammation and contribute to exacerbations and, likely, to disease progression. Many believed that all that was required for bronchiectasis was to implement the well-studied and established therapies already used in cystic fibrosis (CF), such as recombinant DNAse. Such trials have been largely unsuccessful, and the idea that "non-CF bronchiectasis" is a milder version of CF has been largely discredited. Even "non-CF bronchiectasis" is a misnomer—implying a subcategory of a more common condition, when in fact bronchiectasis is far more common than cystic fibrosis. The European Respiratory Society, EMBARC, British Thoracic Society and US Bronchiectasis Research Registry, among others, have recently adopted the more simple name "bronchiectasis".

It is easy to look at the current poor evidence base for treatments in bronchiectasis and the huge challenges we face in clinical management of the disease and to feel frustration at the current state of our medical science. But as Jules Verne said, "Every mistake leads us closer to the truth". Every study and every trial lead us closer to understanding how to diagnose, investigate, phenotype, endotype and manage bronchiectasis.

A good textbook is a concise summary of what we know on a particular topic. A great textbook takes what we know, acknowledges what we do not know and inspires you to find the answers that will improve the science of bronchiectasis and the lives of patients in the future. We hope you find this a great resource in your daily management of bronchiectasis patients and an invaluable guide to the state of the art in bronchiectasis science.

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Introduction

1

Robert Wilson

Bronchiectasis is a morphological term given to the lung condition when there is chronic dilatation of one or more bronchi. Professor Cayol in 1808 brought two specimens to the attention of the famous French physician René Laeanec, who then gave the first clinicopathological description of the disease in 1819 [1]. The term bronchiectasis was introduced later in 1846 by Swaine's translation of Hasse's book on diseases of the organs of circulation and respiration [2].

Until recently there was a generally held belief that bronchiectasis had ceased to be a significant problem in the developed world because improved living standards and the use of vaccines in childhood and antibiotics had reduced the prevalence of infections that caused the condition [3]. I had the honour to give the opening address this year at the first World Bronchiectasis Conference in Hanover. My talk was entitled 'The Renaissance of Bronchiectasis'. This title was chosen because the opposite has occurred, so that whilst figures from different countries vary, there is general agreement that prevalence is increasing and that bronchiectasis becomes more common with older age [4–7]. Bronchiectasis is probably still underdiagnosed, partly because symptoms are indistinguishable from other ill-defined conditions such as chronic bronchitis and also because of the large number of bronchiectasis patients with a primary diagnosis of COPD or asthma [8, 9]. However, it is important to distinguish between clinical and radiological bronchiectasis. Airway dilatation can occur naturally as part of the ageing process, and in asthma dilatation, meeting radiological criteria for bronchiectasis can occur as part of airway remodelling without the clinical picture of cough, sputum and recurrent infections.

The reason for the increase in prevalence is probably multifactorial [10]. CT scans are now easily accessible and allow a radiological diagnosis, when previously

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another clinical diagnosis may have been made. Bronchiectasis is the final pathological pathway of a number of different causes, and some of these may be increasing such as nontuberculous mycobacteria. The population is ageing, and the increased prevalence of clinical bronchiectasis in older age may be ascribed to reduced host defences. Another cause of reduced host defences is the increased therapeutic use of immunosuppression, for example, in cancer and autoimmune disease.

The symptoms of bronchiectasis are a heavy burden and well recognised: chronic productive cough, recurrent chest infections, breathlessness (wheeze), haemoptysis and chest pains. I would draw particular attention to tiredness. Patients with poorly controlled disease are exhausted by the middle of the day when they have difficulty concentrating. When their condition improves with treatment, they report that they 'have got their life back'. In addition to this considerable morbidity, needing frequent hospital visits and longer hospital stays than other chronic diseases, they also have reduced life expectancy [11–14]. About 20 years ago, we fully investigated a group of patients to validate the St George's Respiratory Questionnaire (SGRQ) in bronchiectasis [15].When we looked back at the group after 13 years, about a third had died, 70% directly due to bronchiectasis. Age, SGRQ activity score, chronic *Pseudomonas aeruginosa* infection, airflow obstruction, lung restriction and impaired gas transfer were independently associated with mortality. CT features predicting mortality in multivariate analysis were increased wall thickness, a sign of inflammation and emphysema [12] and in a subsequent study average pulmonary artery diameter, a sign of raised pulmonary artery pressure [16]. Severity indices have been developed (BSI and FACED) which are calculated from easily obtained clinical data, and they can be used to predict risk of mortality, hospital admission and exacerbation [13, 14]. I believe these are very important measurements, and their application should now be explored in clinical practice and when enrolling patients into clinical trials.

When I started working for Professor Peter Cole in 1983, new patients came into our minimal dependency unit at Brompton for 48 h and underwent programmed investigations. We called this the 'host defence workup', and an advantage of the stay with us was several sessions of physiotherapy tuition. Although we now carry out the investigations as outpatients, the approach is unchanged, and this leads to diagnoses that alter management in about a quarter of cases: immune deficiency, allergic bronchopulmonary aspergillosis (ABPA), nontuberculous mycobacterial infection (NTM), inflammatory bowel disease, primary ciliary dyskinesia (PCD), atypical cystic fibrosis, rheumatoid arthritis, aspiration and partial obstruction of an airway [17].

Peter Cole and Rob Stockley proposed the vicious circle hypothesis [18] just before I joined the laboratory. This hypothesis consists of the following circle of events: impaired lung defences permit bacterial infection of the airway mucosa, which stimulates a neutrophilic inflammatory response that becomes chronic when it fails to eradicate the bacteria; the host inflammatory response causes tissue damage, e.g. via proteinase enzymes and reactive oxygen species which overwhelm the body's ability to neutralise them; tissue damage further impairs the lung defences,

allowing bacteria to persist; and so the circle continues and disease may progress and/or spread to a normal bystander lung. The entry point to the circle may differ depending on the aetiology. PCD and hypogammaglobulinaemia impair host defences; NTM is an infection directly causing bronchiectasis; ABPA and inflammatory bowel disease are inflammatory causes of bronchiectasis; and aspiration and smoke inhalation cause direct tissue damage. This hypothesis, ground-breaking when it was proposed, was supported by numerous in vivo and in vitro studies [19–21] and has remarkably stood the test of time so that today we still use it when considering pathophysiology of the disease. However, one weakness of the hypothesis is that it fails to explain why many patients are relatively stable for prolonged periods, whereas in others there is progression of disease.

Our thoughts about microbial pathogenesis also began to change. Instead of thinking about how bacteria invade and damage the host, we began investigating how bacteria evade the host defences and persist in the airway. The damage to the lung in these circumstances comes from the unsuccessful host inflammatory response. My own research was to characterise bacterial compounds which impair ciliary function [22]; other examples are biofilm mode of growth and the alginate gel of pseudomonas which both help the bacteria avoid phagocytes and the antigenic heterogeneity of non-typable *Haemophilus influenzae* which helps the bacterium avoid immune surveillance.

The striking result of all aetiology studies is the large proportion of patients that are idiopathic, usually about half of the cases. I wonder in 10 years' time whether a number of new bronchiectasis aetiologies will have been discovered, and the idiopathic group will shrink, or whether we will find that the idiopathic group contains a large group of patients who have dysregulation of their inflammatory response to infection to explain why bronchiectasis occurs [23]. The proportion of idiopathic cases are influenced by how strictly the definition of postinfection bronchiectasis is made. I think it is difficult to diagnose a postinfection aetiology when a case presents in middle age reporting a historical illness in childhood, but many symptom-free years in between.

We found idiopathic cases, defined as no aetiology found in the 'host defence workup', to have predominately symmetrical lower lobe cylindrical bronchiectasis, they usually presented in early middle age, almost all had chronic rhinosinusitis (suggesting an abnormality throughout the respiratory tract) and symptoms were chronic from the outset. Whereas in postinfection bronchiectasis, defined as symptoms following a defined infection event, bronchiectasis was more unevenly distributed, they presented significantly younger, only about half had chronic rhinosinusitis and initially symptoms were often intermittent [18].

Persistent bacterial infection of the airway mucosa is a key event driving the vicious circle in most cases. Inflammatory bowel disease is the one aetiology in which patients with widespread bronchiectasis produce large volumes of purulent sputum which is often sterile on culture. *H. influenzae* is the most common pathogen, but it is management of *P. aeruginosa* which presents the greatest challenge. Patients presenting with pseudomonas infection usually have more severe and extensive bronchiectasis and more severe airflow obstruction [24]. It seems more

likely that it is patients with severe disease that are susceptible to pseudomonas, rather than pseudomonas being the cause of their severe disease. However, once established, pseudomonas may be carried for life, and overall these patients have worse quality of life [25], increased risk of more rapid progression of disease [26] and reduced life expectancy [12].This is at least in part due to their more severe disease, but also difficulties in managing the infection mean airway inflammation is more difficult to control particularly when ciprofloxacin resistance occurs. The use of inhaled antibiotics, which take time to administer, side effects of frequent oral antibiotics and hospital admission for iv antibiotics all impair quality of life [15]. Management of pseudomonas infection is the area I would highlight as the one which we have most need for new approaches to treatment. There is also much debate about whether an attempt should be made to eradicate pseudomonas when it is first isolated and what that treatment should be [27]. In many cases eradication may appear to have been achieved at the end of treatment, but pseudomonas infection recurs with the next year; and other untreated patients will only culture pseudomonas intermittently. It is not known in either of these scenarios whether these are new strains or chronic infection. A randomised trial is urgently needed to determine whether attempted eradication after first isolation is a successful strategy.

A multidisciplinary team approach is essential in the management of bronchiectasis: physician, radiologist, immunologist, microbiologist, physiotherapist, clinical nurse specialist, dietician, psychologist (psychiatrist), social worker and occupational therapist. Good collaborations are also needed with ENT, thoracic surgery, cystic fibrosis (e.g. milder genotypes), gastroenterology (e.g. reflux, inflammatory bowel disease), rheumatology (e.g. rheumatoid arthritis, Sjogren's syndrome) and a fertility clinic (e.g. primary ciliary dyskinesia, cystic fibrosis, Young's syndrome). The heterogeneity of the bronchiectasis population is a major challenge, in terms of determining both their aetiology and also their presenting problem which may change over time, e.g. a postinfection case may develop ABPA or acquire a NTM infection. This is also a challenge when designing clinical trials, because treatments may not be equally effective in cases with different aetiologies and the severity of disease may affect response to treatment.

If an underlying cause for bronchiectasis has been discovered, e.g. hypogammaglobulinaemia, ABPA and NTM infection, then this should be addressed first. Treatment decisions in bronchiectasis are hampered by the lack of evidence from randomised trials, although thankfully this is beginning to change for long-term antibiotics. The lack of evidence is perhaps best illustrated by physiotherapy, which I have always regarded as the bedrock of bronchiectasis care, yet the best evidence to date comes from a single small crossover study which gave clear results favouring physiotherapy, particularly improvement in results of a cough questionnaire [28]. Treatments to improve mucus clearance are of great interest, and it was disappointing that mannitol failed to meet its primary endpoint [29], although there were sufficient positive results from the study to encourage more work in this area.

We live in a time when there is great concern about antibiotic resistance. Guidelines advise the use of antibiotics that are usually reserved as second line, e.g.

co-amoxiclavulanate and quinolones, and that higher dosages and longer courses are used. This is understandable because the vicious circle hypothesis emphasises the importance of maximal bacterial suppression, recognising that eradication may not be possible. Investigation of the microbiome by molecular techniques will be particularly useful in understanding the effect of antibiotics in this regard. However, present guidelines increase the risk of resistance development, and the lack of sufficient evidence from trials to justify the guidelines weakens the argument for an aggressive antibiotic strategy. Clinicians managing bronchiectasis patients see the benefit of this strategy in individual cases, but more research is urgently needed.

The concentration of oral antibiotics reaching the airway mucosa is low, particularly for beta lactam antibiotics that penetrate cells and secretions poorly. This difficulty is increased due to scarring of the airway and excess secretions harbouring many millions of bacterial per millilitre. Inhaled antibiotics are therefore attractive, delivering high concentrations direct to the mucosa, although there may be difficulties of distribution due to mucus plugging and airway distortion. This approach should lessen the risk of resistance, although this needs to be carefully monitored.

Antibiotic prophylaxis has been recognised to improve bronchiectasis symptoms since the early study by the MRC [30]. However, to justify this approach, with the inevitable risks of side effects, particularly gastrointestinal, and antibiotic resistance, then a reduction in exacerbations should be demonstrated. This has not proved straightforward, even when high dosages of antibiotic are used [31]. More recent studies using inhaled antibiotics have shown significant reductions in bacterial numbers cultured from sputum and in exacerbation frequency [32–35]. The study by Howarth and colleagues was of particular interest because it showed benefits only in patients using the antibiotic regularly. It was a salutary lesson that even under clinical trial conditions, patients did not take the antibiotic as frequently as prescribed. This emphasises that it will not just be the potency of the antibiotic that is important but also its distribution in the bronchial tree; any side effects, e.g. cough and wheeze, that occur; and how easy/convenient the delivery machine is to use.

The vicious circle hypothesis emphasises the importance of controlling the inflammatory response. Physiotherapy achieves this by improving clearance of secretions containing bacteria and their products which attract neutrophils into the airway, antibiotics achieve it by killing bacteria, and a third approach is to reduce inflammation directly. Macrolide antibiotics have been shown in three randomised, placebo-controlled trials to reduce exacerbation frequency [36–38]. They are thought to do this by their anti-inflammatory rather than antibacterial properties. Other anti-inflammatory approaches, such as inhaled steroids, have been less successful [39], but this is an active area of research, e.g. neutrophil elastase inhibitors.

I have emphasised that more studies are needed to improve the evidence base for our investigation and management of bronchiectasis. For these to be successful, they must enrol a more homogeneous population. One approach has been to enrol patients for antibiotic trials by aetiology, e.g. idiopathic and postinfective [33, 35]. These cases are thought to have intact host defences, and their disease process is

thought to be driven by bacterial infection. The success of this approach is dependent on the extent of investigations performed to define the aetiology. A second approach might be to define patient phenotypes as suggested by Alberti and colleagues [40]. These authors used cluster analysis of more than a thousand patients from European databases to define four groups that had different quality of life, exacerbation frequency and mortality: chronic pseudomonas infection, other chronic infection, daily sputum production and dry bronchiectasis. A third approach might base enrolment on different stages of the vicious circle hypothesis: mucus clearance, e.g. daily sputum volume above a certain level; type of bacterial infection, e.g. pseudomonas or non-pseudomonas; inflammation, e.g. a marker of inflammation such as free neutrophil elastase in sputum; and disease severity (lung damage), e.g. based on severity assessed by CT scan together with severity indices (BSI and FACED) [13, 14].

I am very excited that our current knowledge of bronchiectasis has been brought together in this textbook. Experts in each area will describe optimal medical management: how to investigate to exclude treatable causes, the best approaches to physiotherapy and the effectiveness of pulmonary rehabilitation, which antibiotics and what treatment regimens to best treat exacerbations, when to use antibiotic prophylaxis and the options available and who will benefit from anti-inflammatory approaches. In addition, which patients should we refer for consideration of surgery and transplantation, and when should we refer to allied disciplines? I am sure that an additional benefit will be that with this knowledge, the priorities for future research will become clearer. With the arrival of this book, the time for the renaissance of bronchiectasis truly feels to have arrived!

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Imaging of Bronchiectasis

2

Mario Silva, Gianluca Milanese, and Nicola Sverzellati

2.1 Chest Radiography and Bronchography

Early-stage bronchiectasis is variably detectable depending on reader experience. Notably in this phase with subtle symptoms, the diagnosis is ideal because the therapy would be more beneficial. In case of severe bronchiectasis, radiographic signs are quite obvious, though inaccurate. Even in patients with symptoms of chronic bronchitis, the sensitivity of radiography is scant, namely, about 50% compared to bronchography [1].

Signs of bronchiectasis on chest radiography are usually depicted with more severe abnormalities. The signs of bronchiectasis include:

- *Linear markings* radiating from the hila that reflect luminal dilation and variable bronchial wall thickening. This finding is also called "tram track" sign because the linear markings might run parallel to each other, resembling a railway (Fig. 2.1a). They may be the only finding in patients with cylindrical bronchiectasis, and moreover, it also may be seen with bronchial wall thickening in the absence of bronchiectasis. Therefore, the "tram track" sign is quite inaccurate.
- *Ring sign* mirrors bronchial thickening when the major axis of bronchiectasis runs parallel to the radiation beam (Fig. 2.1a). Signet ring and tram track signs essentially reflect the same anatomic abnormality but in two different projective situations. Air-fluid level can be seen within the ring in case of abundant bronchial secretion.
- *Tubular or branching opacities* reflect the mucus plugging within bronchial lumen (Fig. 2.1b), variably represented in different severity of bronchiectasis and different moments for the same patient [2].

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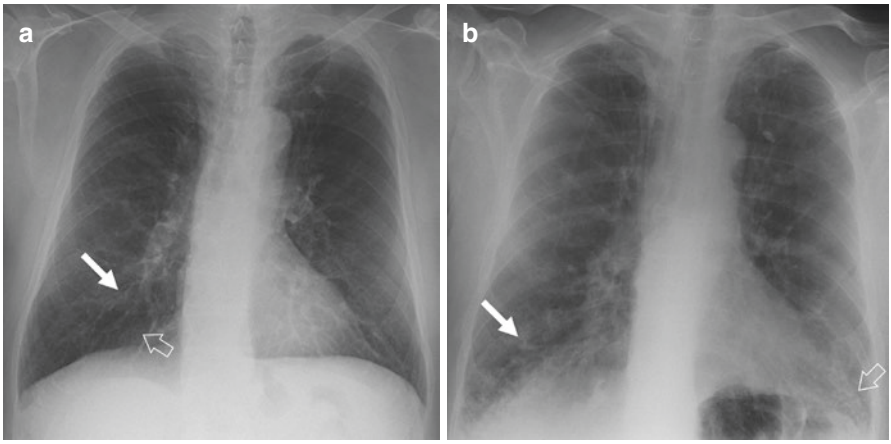

Fig. 2.1 (**a**, **b**) Chest radiograph of a patient with bronchiectasis and its infectious acutization. (**a**) Chest radiographs show linear markings with parallel outline (*arrow*) and ring-like opacities (*open arrow*), reflecting bronchiectasis, respectively, perpendicular and parallel to the X-ray beam. (**b**) Chest radiograph shows linear/branching opacities (*arrow*) and nodular opacities (*open arrow*) with basal predominance during infectious acutization of bronchiectasis

- *Variation of pulmonary volume* either reduction or increase can be seen in patients with bronchiectasis, according to the specific cause. Volume increase is associated with bronchiectasis in obstructive pulmonary disease. Conversely, asymmetric volume reduction with parenchymal opacification is associated with segmental or lobar atelectasis, which usually associates with fissural displacement and/or diaphragmatic obscuration. Volume reduction and reticular opacities are seen with restrictive pulmonary disease associated with fibrotic interstitial lung disease.
- *Vascular structures* may be increased in size and may show fuzzy outline because of contiguous peribronchial inflammatory infiltrates and chronic fibrotic evolution.

Other signs such as pleural thickening, scarring, and formation of bulla can be variably seen as result of chronic inflammation and recurrent exacerbation.

Bronchography shows elegantly the abnormalities of bronchial outline as well as the paucity of bronchial divisions, and it can consistently differentiate cystic bronchiectasis from less severe degree of bronchial distortion. It was preferred over radiography for characterization of bronchial anatomy, until the widespread diffusion of high-resolution computed tomography (HRCT) [3].

2.2 Chest CT and HRCT

Computed tomography, notably HRCT, is the current reference standard for pulmonary imaging in the majority of respiratory diseases, including bronchiectasis. The technical requirements for dedicated imaging of the lung by HRCT are the

following: thin-section acquisition (1 mm), high-spatial-frequency reconstruction, and appropriate window setting. These are the paramount technical features for accurate characterization of bronchial wall distortion and, in particular, thickening, which might be otherwise overrated. Notably, thicker section, low-spatial-frequency reconstruction, and overly narrow (<1000 HU) or high (> −250 HU) window settings would render blurred interface between the bronchial wall (internal and external aspects) and surrounding air, resulting in artificial bronchial wall thickening [4]. Volumetric acquisition allows the utmost confidence in diagnosis of bronchiectasis [5]. Conversely, serial CT suffers from possible overlooking areas of focal bronchiectasis, located exclusively in areas skipped by interspacing between slices. On serial acquisition, bronchiectasis might be referred as cystic lesions, and vice versa, because the gap between slices does not allow to assess the continuity of bronchial structures. On the other hand, volumetric display and multiplanar reconstruction increase confidence in the differential between bronchiectasis and a range of reticular and cystic abnormalities, in particular honeycombing. Volumetric acquisition renders the volumetric characteristics of tubular (e.g., bronchi) or rounded isolated (e.g., cysts) structures. Of note, cystic bronchiectasis may be misinterpreted as cyst if the bronchus between subsequent cystic enlargements is near normal, despite volumetric acquisition.

Small cylindrical bronchiectasis in a single pulmonary segment appears in a significant percentage of the healthy population; therefore, they should not be considered [6]. However, the definition of minor positive finding for bronchiectasis is subject of debate, notably in association with the underlying chronic clinical condition. For instance, the definition of minor bronchiectasis in a chronic obstructive pulmonary disease (COPD) population was represented by slightly dilated or nontapering airways that involved less than four segments [7]. In patients with emphysema, minimal bronchiectasis was defined by involvement of one bronchopulmonary segment or even part of it [8]. A comprehensive description of bronchiectasis in different clinical scenarios was provided by Tan et al. who reported the following specific prevalences: 19.9% in normal never smoker without respiratory symptoms, 19.9% in smokers, 14.1% in patients with mild COPD, 22% in patients with moderate COPD, and 35.1% in patients with severe or very severe COPD [9]. They used the definition of bronchiectasis related to the mild increase in the bronchial–arterial ratio and argued this method could be overly sensitive. The bronchial–arterial ratio is particularly good to provide a standardized metric. However, the ratio could be overrated from pathologies involving the artery, as it was demonstrated in COPD. Diaz et al. reported that the majority of cases of increased bronchial–arterial ratio in COPD patients were related to a reduced size of the blood vessel [10]. The same group suggested that such ratio might be inappropriate even in healthy never smokers [11]. Therefore, there is no consensus on the definition of the minimal HRCT finding that should be deemed disease per se. In clinical practice, the integration with complete clinical history would allow an optimal accuracy in reporting HRCT findings.

The major anatomic detail of HRCT comes with the relevant concern of significantly increased radiation exposure that should be balanced with the clinical advantage of such imaging method, especially in case of young and female patients.

Low-dose HRCT should be considered in selected cases. Clinical low-dose technique (≈6 months of background exposure) can reduce the radiation exposure by about five times compared to standard HRCT (≈2 years of background exposure), namely, to the equivalent of about 15–20 chest radiographies (≈10 days of background exposure) [12].

Follow-up of bronchiectasis is not recommended by HRCT, yet bronchiectasis evolution was described in association with low BMI and infection from *Pseudomonas aeruginosa* [13]. Side-by-side comparison between baseline and follow-up scan might be the optimal review layout to assess bronchiectasis evolution with minimal methodological bias [14].

HRCT semiology of bronchiectasis includes both direct and indirect signs. Direct signs of bronchiectasis reflect morphological abnormalities of the bronchial wall, namely:

- *Bronchial dilatation*: minor cylindrical dilation is usually seen as absence of normal tapering (Fig. 2.2a). This is best depicted in airways that run parallel to the axial plane, such as lower segments of upper lobes and middle lobe. In case of bronchial dilation, the ratio between the diameters of bronchial lumen and its homologous pulmonary artery exceeds 1 [15]. The disproportion between bronchus and artery recalls the "signet ring" appearance in lower lobes and apical segment of upper lobes, where the bronchovascular bundle runs perpendicular to the axial plane. Minor bronchiectasis can also be detected when airways are visible within 1 cm of costal pleura [16]. Varicose and cystic bronchiectasis are quite obvious on HRCT [17] (Fig. 2.2b, c). The former is characterized by a beaded appearance, whereas the latter is seen as thin-walled cystic spaces variably associated with fluid levels. In cystic bronchiectasis, the accompanying

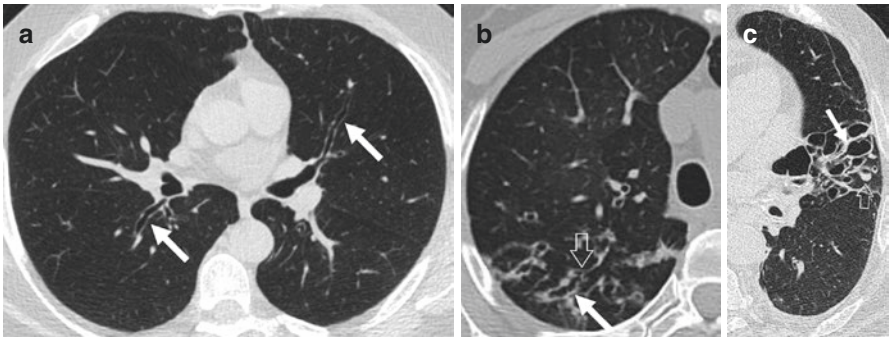

Fig. 2.2 (**a**–**c**) Bronchiectasis characterized by computed tomography into the three main morphological types. (**a**) Cylindrical bronchiectasis on CT is seen as non-tapering of bronchial lumen (*arrows*). (**b**) Varicose bronchiectasis characterized by luminal enlargement (*arrow*) with interposed stenosis (*open arrow*). (**c**) Cystic bronchiectasis characterized by balloon-like dilatation of the bronchial lumen (*arrow*) and air–fluid levels from mucus deposition (*open arrow*)

pulmonary artery can be obliterated; thus, the differential might be challenging with bullous emphysema and cystic lung diseases. Expiratory scan can be used for the differential because bronchiectasis tends to collapse, whereas other cystic abnormalities do not [18].

Bronchiectasis associated with fibrotic interstitial lung disease is usually referred as "traction bronchiectasis." By definition, they are non-tapering airways surrounded by abnormal lung parenchyma such as ground-glass and/or reticular opacity. Therefore, the term traction bronchiectasis should be utilized only in lung fibrosis. Their predominant distribution depends on the underlying subtype of lung fibrosis (e.g., basal predominance in usual interstitial pneumonia, upper lobes predominance in sarcoidosis). Traction bronchiectasis may also vary in severity, which has a strong prognostic value.

- *Bronchial wall thickening*: this sign is variably seen, and it is possibly reversible because it likely reflects the specific inflammatory status of a bronchial portion in a specific moment. Standard definition of bronchial thickening on CT is not obvious. In case of mild bronchiectasis, bronchial thickening can be defined when the luminal diameter is <80% of external diameter [19]. However, this definition is not suitable for larger bronchiectasis. In a study about COPD-related bronchiectasis, the bronchial wall thickness (graded on a qualitative 5-point scale) was significantly associated with severity of bronchiectasis [7].
- *Airway plugging*: focal opacities or also elongated finger-in-glove opacification of bronchial lumen can be seen in bronchiectasis; this reflects the mucoid impaction at any bronchial generation, notably in the central airway. Mucus impaction can appear also as Y- or V-shaped opacities that reflect thickening of the bronchial wall. Centrilobular nodules (both solid and subsolid) attached to fine Y- or V-shaped opacities represent the so-called tree-in-bud pattern that reflects exudative filling in small airway and airspace [20]. It is important to differentiate between peripheral mucus plugging and central mucoid impaction, because the latter is specific for allergic bronchopulmonary aspergillosis (ABPA).

Diffuse or localized parenchymal abnormalities can be associated with bronchiectasis, reflecting abnormalities in the airspace, such as:

- *Mosaic attenuation pattern*: areas of decreased attenuation that have been attribute to obstruction from obliterative bronchiolitis. Vascular paucity (reduction in number and caliper of vessels) is a key finding for differential of subtle mosaic appearance and could be attributed to hypoxic vasoconstriction in areas with poor ventilation [21]. Mosaic attenuation is mostly associated with overt bronchiectasis, but it can also be seen as isolated CT finding. Expiratory scan enhances the density gradient between areas of air trapping and the normal lung (Fig. 2.4c), which allows differential with panlobular emphysema [22].

- *Volume loss*: volume loss with consolidation can be the consequence of chronic inflammation from bronchiectasis and consequent peribronchial fibrosis. In this case, airways appear exceptionally crowded within parenchymal collapse. Conversely, volume loss is the cause of bronchiectasis, namely, traction bronchiectasis, in fibrotic interstitial diseases. Parenchymal reticulation and vascular or fissural distortion are hallmark of traction bronchiectasis that yield specific prognostic value.
- *Thickening of interlobular septa*: this sign was found more frequently in lobes with bronchiectasis compared with lobes without bronchiectasis, in a cohort of patients with idiopathic bronchiectasis. Allegedly, the prominent inflammatory infiltration into the submucosa of bronchiectasis might lead to lymphatic congestion and, thus, thickening of the interlobular septa [23]. Noteworthy, interlobular and intralobular thickening is also seen in fibrotic interstitial diseases with traction bronchiectasis, again to be differentiated from other forms of bronchiectasis.

Bronchiectasis can associate with hemoptysis. Bronchiectatic hemoptysis ranges from minor sporadic event to major life-threatening hemorrhage. Hemorrhage is more frequently derived from systemic bronchial or non-bronchial arteries, while it is sporadically caused by pulmonary arteries [24]. Angiographic CT with intravenous injection of contrast agent plays a major role in imaging the mediastinum, notably the vascularization of bronchiectasis from systemic or pulmonary arteries (Fig. 2.3) [25]. Angiographic CT has even higher yield than conventional

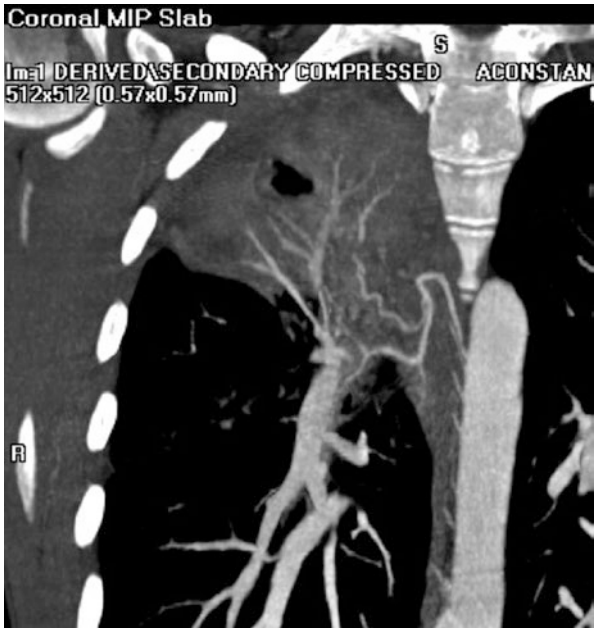

Fig. 2.3 Angiographic CT of the chest in coronal reconstruction of a patient with recurrent severe hemoptysis. The opacification of bronchial arteries (see origin from descending aorta) shows the vascular enlargement that cause recurrent hemoptysis

angiography because it provides better depiction and traceability of the bronchial arteries [26]. Angiographic CT is used for specific detection of arteries causing hemoptysis with the aim of planning endovascular treatment [27].

2.3 Magnetic Resonance Imaging

Lung imaging by magnetic resonance (MR) has been long investigated, and efforts are conspicuous especially in pediatric population to avoid radiation exposure.

MRI has significantly longer times of acquisition and limited spatial resolution compared to HRCT. Motion artifacts (e.g., cardiac pulse, respiratory movement of diaphragm) are among the limitations of MRI in the chest. Of note, the main limitation of MR in imaging the lung derives from low concentration of hydrogen (the atom that provides the MR signal) and abundance of oxygen (an atom that causes noise). However, bronchiectasis is typically characterized by increased density of lung structure; therefore, MR found its indication in specific cases of bronchiectasis. In particular, MR is used in pediatric patients with cystic fibrosis because the significant chronic wall thickening and abundance of mucus bring more "resonance substrate" in the pulmonary volume. In these patients, MR is mandatory because the radiation exposure from HRCT would significantly increase the risk of radio-induced malignancy. The potential advantage of MR lays in the possibility to provide "more than morphological" information about the bronchial wall. However, MR is still quite far from clinical applicability for the assessment of bronchiectasis in adulthood.

2.4 Etiology of Bronchiectasis and Typical Radiological Findings

Ancillary CT signs can suggest the etiology of bronchiectasis in less than half of patients. Typical CT features of one etiology can be seen, without being exclusive. Idiopathic bronchiectasis is more common in lower lobes [28]. However, the differential between idiopathic bronchiectasis and bronchiectasis associated with other cause is usually left to clinical integration because radiologic features are not accurate for this purpose. Thereafter, typical CT features of different bronchiectasis etiologies are reported, which could be used to pitch differential diagnosis (Table 2.1).

2.4.1 Allergic Bronchopulmonary Aspergillosis (ABPA)

Bronchiectasis in ABPA is predominantly apical and centrally located. Typically, segmental and subsegmental bronchi are enlarged and filled with dense mucus that represents the chronic airway colonization from *Aspergillus fumigatus* with deposition of calcium salts (expectoration of brown plugs can be referred). ABPA should

Table 2.1 Summary of cause of false-negative or false-positive finding for diagnosis of bronchiectasis on HRCT

Cause of bronchiectasis	HRCT finding
Allergic bronchopulmonary aspergillosis (ABPA)	Central and apical bronchiectasis, mucus impaction seen as "finger-in-glove" sign, high-density mucus plugging
Swyer–James (McLeod) syndrome	Asymmetric hyperlucency that reflects unilateral air trapping
Tracheobronchomegaly (Mounier–Kuhn syndrome)	Excessive dilatation of the trachea and main bronchi
Mycobacterium avium-intracellulare complex	Tree-in-bud opacities with predominant distribution in the right middle lobe and lingula, progressive slow evolution
Primary ciliary dyskinesia	Association with situs viscerum inversus in 50% of cases
Fibrotic interstitial lung diseases	Bronchiectasis is mostly associated with parenchymal reticulation or ground-glass opacities, fissure distortion, and volume loss; differential with honeycombing

be suspected in asthma and cystic fibrosis, albeit plugging is not exclusive of aspergillus colonization (skin test should be prompted in these scenarios). Central plugs resemble a glove finger ("finger-in-glove sign") (Fig. 2.4) and are variably associated with small airway filling revealed by tree-in-bud opacities. Chronic inflammation may be associated with lymph node enlargement and calcification, which can also occur in chronic granulomatous or professional diseases (e.g., tuberculosis, sarcoidosis, silicosis, etc.).

2.4.2 Nontuberculous Mycobacterial Infection

Bronchiectasis in nontuberculous mycobacterial infection is usually minor and oligosymptomatic at early stage. Typically, but not exclusively, bronchiectasis occur in the middle lobe and lingula (this distribution is also known under the name "Lady Windermere syndrome," derived from Oscar Wilde comedy), and they are associated with nodular component that reflects exudative process in small airway and airspace, namely, the tree-in-bud pattern (Fig. 2.5). Bronchial nontuberculous mycobacteriosis is associated with colonization from *Mycobacterium avium complex* (MAC) [29]. The early diagnosis is quite challenging because of the unspecific clinical presentation; radiology is useful in depicting minor bronchiectasis and its slow progression. Among signs of progression, severity of bronchiectasis and associated atelectasis should be always carefully interpreted. Mosaic perfusion on inspiratory scan is a common finding, which is characterized as air trapping on expiratory scan.

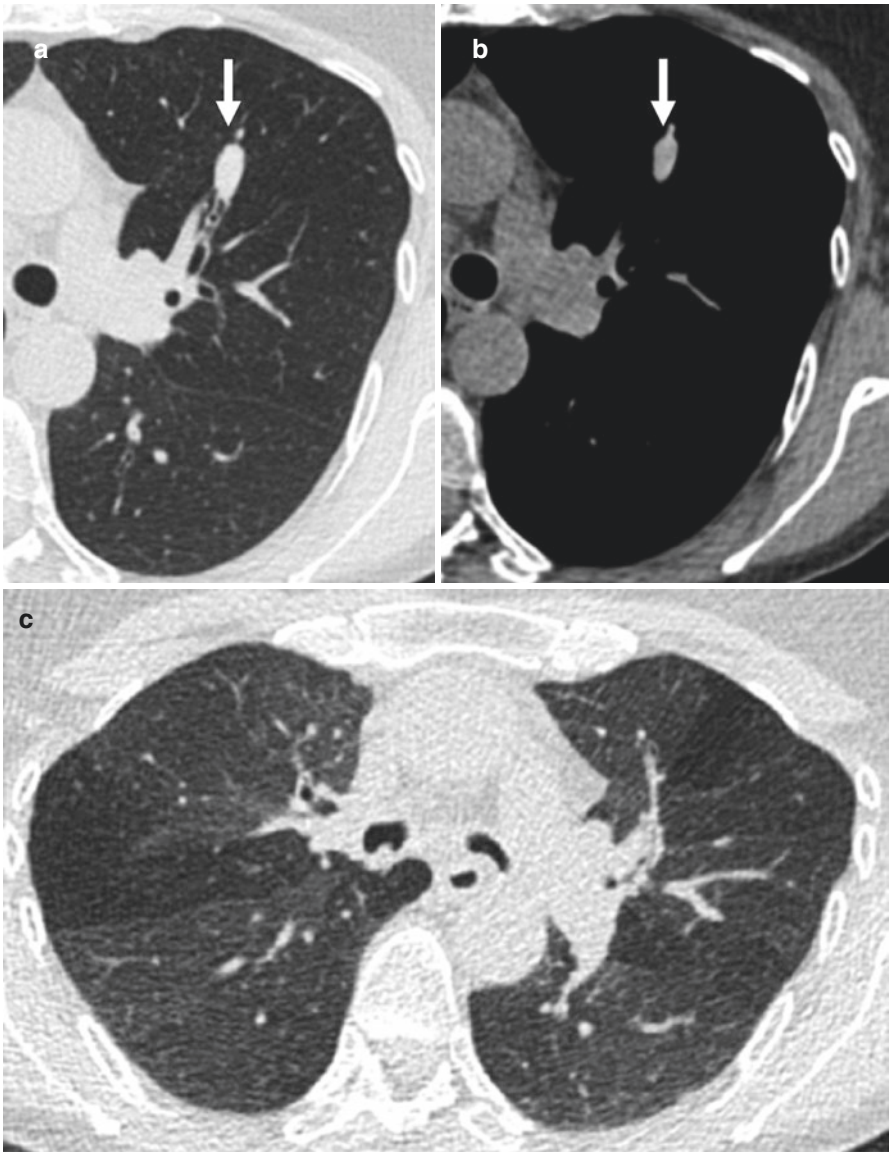

Fig. 2.4 (**a**–**c**) Mucus impaction in allergic bronchopulmonary aspergillosis (ABPA). (**a**) Large tubular intrabronchial opacity (*arrow*) in anterior segmental bronchus of the left upper lobe, which reflects central mucus impaction in ABPA. It can also be called "finger-in-glove sign" according to the resemblance with glove finger. (**b**) Mediastinal window shows the high density of the mucus impaction (*arrow*), an ancillary sign of ABPA. (**c**) Expiratory acquisition enhances mosaic attenuation of lung parenchyma, which is caused by air trapping. It is seen as triangular darker areas of the lung

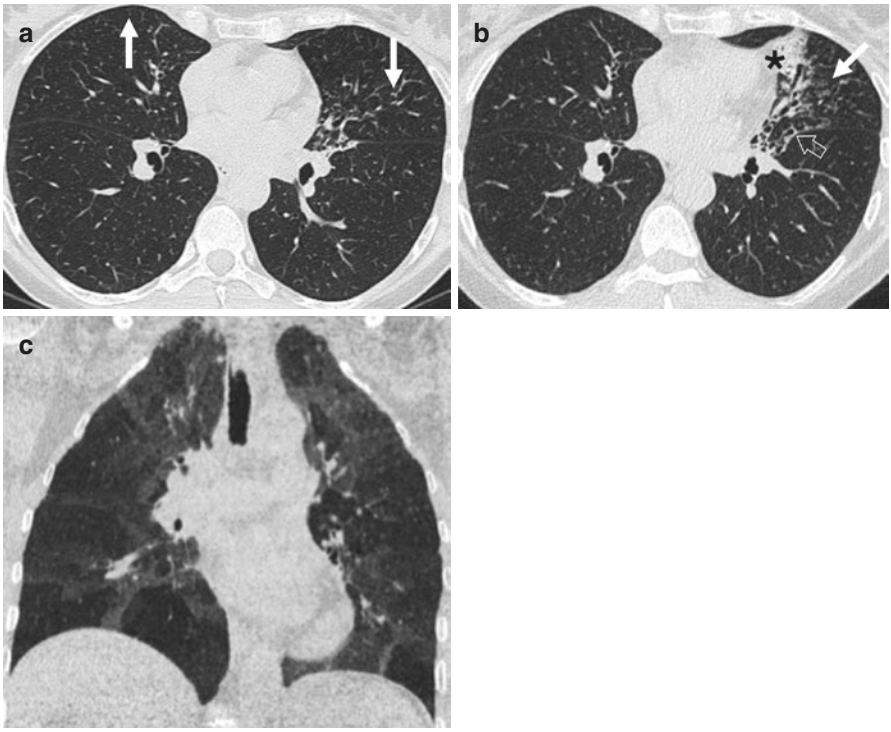

Fig. 2.5 (**a**–**c**) Slow temporal evolution of peripheral mucus plugging in nontuberculous mycobacteriosis from *Mycobacterium avium* complex (MAC). (**a**) Year 2008, small nodular intrabronchial opacities (*arrow*) are seen in the right middle lobe and lingula, along with minor bronchiectasis. (**b**) Year 2016, slow progression of parenchymal signs in barely symptomatic patients allows for clinical suspicion of nontuberculous mycobacteriosis which was confirmed *Mycobacterium avium* complex (MAC). Tubular and tree-in-bud opacities persist and increase (*arrow*), along with bronchiectasis progression (*open arrow*) and onset of circumscribed parenchymal consolidation (*asterisk*). (**c**) Year 2016, expiratory acquisition with coronal reconstruction of lung parenchyma shows air trapping, which is seen as triangular darker areas of the lung

2.4.3 Swyer–James Syndrome

The Swyer–James syndrome is caused by constrictive bronchiolitis that follows viral or mycoplasma respiratory infections in the infancy. The associated developmental deficiency of the airspace is associated with hyperinflation and hypovascularization. From the radiological perspective, it is usually suspected when asymmetric hyperlucency is seen as the result of unilateral air trapping, with segmental, lobar, or diffuse distribution [30]. Despite the hyperlucency from air trapping, lung volume in the affected lung is supposed to be reduced. Bronchiectasis and atelectasis may be associated; however, it is usually clinically silent.

2.4.4 Primary Ciliary Dyskinesia

Primary ciliary dyskinesia can be readily suggested when bronchiectasis is associated with *situs viscerum inversus* (Fig. 2.6). However, only 50% of primary ciliary dyskinesia associate with organ displacement. Because primary ciliary dyskinesia is an autosomal recessive disorder that involves ciliary development, more systemic abnormalities are typically associated with pulmonary findings, namely, sinusitis, otitis, rhinitis, and reduced motility of spermatozoa [31]. Radiological findings are predominantly basal, with isolated bronchiectasis variably associated with parenchymal consolidation and/or segmental atelectasis [32].

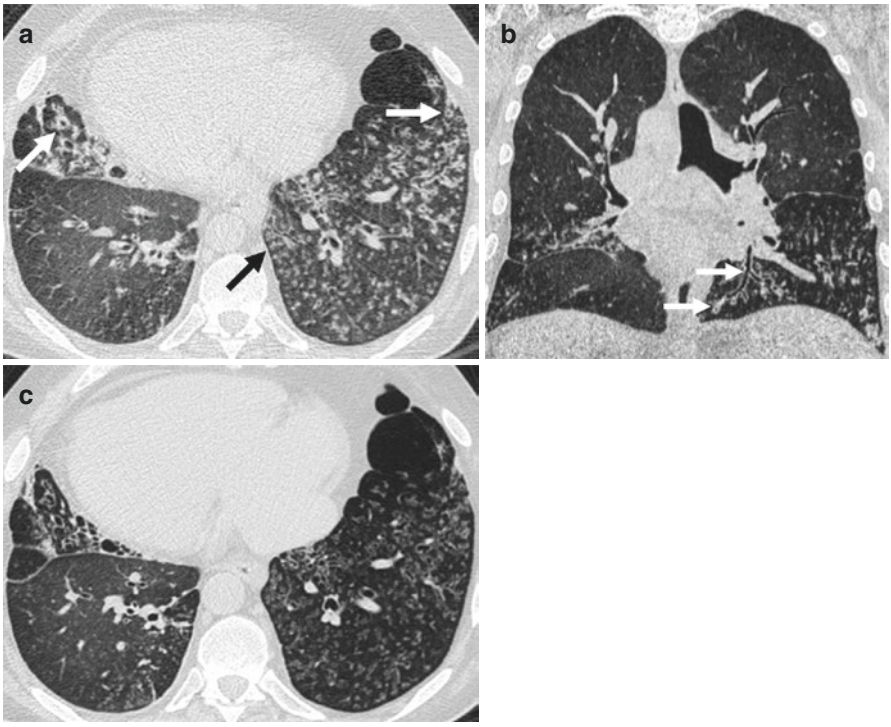

Fig. 2.6 (**a**–**c**) Primary ciliary dyskinesia in a patient with situs viscerum inversus. (**a**) Acute infection of diffuse bronchiectasis and bronchiolectasis is seen as centrilobular nodules and tree-in-bud opacities (*black arrow*) with substantial sparing of subpleural parenchyma, which are associated with severe wall thickening (*white arrow*). (**b**) Inspiratory coronal reconstruction shows a bronchiectasis with wall thickening and peripheral mucus plugging in the left lower lobe (*arrow*). (**c**) Follow-up after therapy (time range 7 months) shows reduction of wall thickness and tree-in-bud opacities

2.4.5 Hypogammaglobulinemia

Bronchiectasis in hypogammaglobulinemia develops predominantly in lower and middle lobes. They are mostly cylindrical in shape but with severely thickened walls. Bronchiectasis is a possible pulmonary complication of acquired hypogammaglobulinemia in patients under immunosuppressant after kidney transplantation.

2.4.6 Common Variable Immunodeficiency

Common variable immunodeficiency is associated with bronchiectasis in about 50% of cases. Bronchiectasis usually shows wall thickening and associates with air trapping. Reticular opacities that reflect granulomatous fibrosis associate with bronchiectasis [33].

2.4.7 Tracheobronchomegaly (Mounier–Kuhn Syndrome)

Tracheobronchomegaly is centrally located; as per the name, dilated trachea and great bronchi are a constant finding with typical balloon appearance [34]. Tracheobronchomegaly can be seen on radiography, notably when the transverse caliper of trachea exceeds 25 mm in men and 21 mm in women [35]. Broader extent to the larynx and/or peripheral airways can be seen. Mucosal herniation should be expected among cartilage rings of the trachea (also referred as "tracheal diverticulosis") that reflects increased mucosal compliance from decreased elastic component. Accordingly, the airways collapse under expiratory effort. On CT, bronchiectasis of tracheobronchomegaly has thin walls, which is quite unique compared to any other cause of bronchiectasis [36]. Tracheobronchomegaly is mainly a congenital disease, but it can rarely be seen also in association with Ehlers–Danlos syndrome, cutis laxa, ankylosing spondylitis, and rheumatoid arthritis.

2.4.8 Williams–Campbell Syndrome

The Williams–Campbell syndrome is a congenital disease with specific deficiency of airway cartilage in subsegmental bronchi. Therefore, imaging findings are peculiar with cystic bronchiectasis and bronchial wall thickening, from the fourth bronchial generation up [37]. Moreover, expiratory CT highlights air trapping caused by excessive collapse of smaller cartilaginous bronchi.

2.4.9 Fibrotic Interstitial Lung Disease

Fibrotic interstitial lung disease is associated with traction bronchiectasis [38]. Traction bronchiectasis is not specific of a particular fibrotic interstitial lung disease but rather common in this spectrum of diseases. Traction bronchiectasis is different

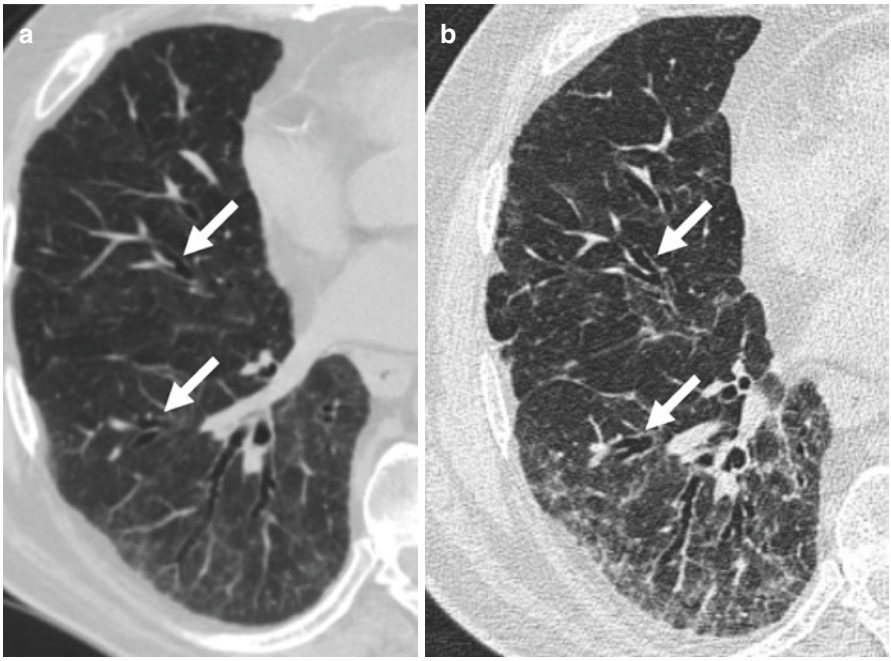

Fig. 2.7 (**a**, **b**) Traction bronchiectasis in fibrotic interstitial lung disease. Temporal progression of traction bronchiectasis (*arrows*) is seen during a 6-year follow-up ((**a**) year 2010, (**b**) year 2016), along with increase of direct parenchymal signs of interstitial fibrosis, such as reticulation and ground-glass opacity that in this subject showed subpleural distribution and lower lobe predominance

from bronchiectasis associated with chronic bronchial infection because it is essentially caused by stretching from parenchymal distortion. Typically, there is obvious association with signs of parenchymal fibrosis such as reticulation, ground-glass opacity, and honeycombing, as well as with other signs of pulmonary fibrosis, for instance distortion of fissures and of pulmonary vessels.

The tight correlation between severity of parenchymal fibrosis and traction bronchiectasis has been described in idiopathic pulmonary fibrosis (IPF) [39]. The profusion of fibroblastic foci in IPF is positively associated with severity of bronchiectasis, without causal connection between each other [40]. In case of IPF, subjects with traction bronchiectasis within possible UIP pattern (Fig. 2.7) and patients with typical honeycombing and/or histological confirmation of IPF showed similar response to therapy [41].

Fibrotic interstitial lung disease secondary to collagen vascular disease may show traction bronchiectasis, notably in rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), scleroderma, and Sjogren syndrome [42]. Furthermore, bronchiectasis can be seen in RA as isolated finding, namely, independently from fibrotic distortion of lung parenchyma. Likewise, traction bronchiectasis in scleroderma can be overly disproportionate compared to the severity of signs of parenchymal fibrosis.

2.5 Radiological Scores

Radiological scores to grade the degree and extent have been described in the second half of the previous century, both for chest radiograph [43] and HRCT [44]. The Reid classification encompasses three grades of severity based on morphological description of the pattern of bronchial wall distortion [43]. Bronchography and CT are more accurate than radiography in the definition of each category. The three-grade Reid classification is reported below:

- *Cylindrical bronchiectasis*: mild bronchial dilatation that does not compel distortion of bronchial outline; parallel walls and uniform caliber are preserved.
- *Varicose bronchiectasis*: bronchial outline is modified by subsequent enlargement and focal constrictions, resulting in irregular shape and more severe obstruction and obliteration of small airways.
- *Cystic* (*saccular*) *bronchiectasis*: the extreme morphological modification of bronchial structure is characterized by ballooned appearance (diameter can exceed 2 cm) and reduction of bronchial divisions.

The Bhalla score is based on the CT analysis of bronchiectasis associated with cystic fibrosis in a relatively little population of children with cystic fibrosis [44]. Despite its specific methodological derivation, the Bhalla score is used for description of bronchiectasis from any etiology. An explanation for the widespread application of the Bhalla score can be found in its descriptive structure that allows comprehensive characterization (systematic description of bronchiectasis features and pulmonary abnormalities beyond bronchiectasis) and relatively easy applicability (Table 2.2).

The Reiff score is derived from modification of the Bhalla score, notably with apportioning of extent on lobar basis, for six lobes [45]. The individual lobe score according to Reiff et al. is reported in Table 2.3. The total extent of bronchiectasis throughout the lungs is calculated as the sum of the six individual lobe scores. Furthermore, this score includes:

- *Morphological description* of bronchiectasis according to Reid (e.g., cylindrical, varicose, and cystic) [43].
- *Lobar-wise distribution* of bronchiectasis according to lobar distribution:
  - Predominantly upper lobe
  - Predominantly middle lobe
  - Predominantly lower lobe
  - Middle and lower lobes equally involved
  - Widespread 5–6 lobes involved
- *Axial-wise distribution* of bronchiectasis divided into three categories, namely, central, peripheral, or mixed. The distinction between central and peripheral bronchial involvement was set according to a point midway between the hilum and the chest wall [46].

Table 2.2 Detailed description of the radiological score proposed by Bhalla et al. (Adapted from [44])

Category	1	2	3
Severity of bronchiectasis	*Mild*: luminal diameter slightly larger than diameter of the homologous artery	*Moderate*: luminal diameter 2–3 times the diameter of the homologous artery	*Severe*: luminal diameter >3 times the diameter of the homologous artery
Peribronchial thickening	*Mild*: bronchial wall thickness equal to the diameter of the homologous artery	*Moderate*: bronchial wall thickness ≤2 times the diameter of the homologous artery	*Severe*: bronchial wall thickness >2 times the diameter of the homologous artery
Extent of bronchiectasis (n of involved segments)	1–5	6–9	>9
Extent of mucus plug (n of involved segments)	1–5	6–9	>9
Sacculation or abscesses (n of involved segments)	1–5	6–9	>9
Bronchial generation with bronchiectasis and/or mucus plug	≤fourth generation	≤fifth generation	Diffuse bronchiectasis including distal bronchi
Bullae: distribution and total number	Unilateral ≤4	Bilateral ≤4	>4
Emphysema (n of involved segments)	1–5	>5	ND
Extent of collapse and/or consolidation	Subsegmental	Segmental or lobar	ND

ND Not defined; the value "0" is omitted in the table because it always reflects absence of the mentioned category

Table 2.3 Detailed description of the radiological lobar score proposed by Reiff et al. [45]

Category of individual lobar involvement	1	2	3
Extent of bronchiectasis	One or partial bronchopulmonary segment involved	Two or more bronchopulmonary segments involved	ND
Severity of bronchiectasis	Luminal diameter <2 times the diameter of the homologous artery	Luminal diameter 2–3 times the diameter of the homologous artery	Luminal diameter >3 times the diameter of the homologous artery
Peribronchial thickening	Bronchial wall thickness 0.5 the diameter of the homologous artery	Bronchial wall thickness 0.5–1 the diameter of the homologous artery	Bronchial wall thickness >1 the diameter of the homologous artery

ND Not defined; the value "0" is omitted in the table because it always reflects absence of the mentioned category

Both the classifications from Bhalla and from Reiff have limitation in that patients can have similar severity scores either from severe localized disease or from widespread mild disease. Notably, similar radiological scores would represent diverse etiologies with different prognostic implication. Indeed, the amount and extent of pathology as scored by radiology do not always reflect the rate of airway damage, namely, the disease activity. More recently, multidimensional scores have been proposed by combination of clinical and radiological input with the aim of predicting the clinical outcome and, possibly, to serve as outcome measure in clinical trials. In particular, radiological input was included in the FACED score [47] when presence of ≥3 lobes with bronchiectasis was reported according to the radiologic criteria from Naidich et al. [48], with exclusion of small isolated single bronchiectasis. Furthermore, the bronchiectasis score index (BSI) also includes a radiological input that is expressed by the presence of ≥3 lobes with bronchiectasis as scored by a modified Reiff method [49]. Compared to the FACED score, the BSI also informs on annual risk of mortality, including the progressive additional risk derived from hospitalization.

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Epidemiology

3

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3.1 Epidemiology of the Disease

Bronchiectasis is not itself a disease, but rather the result of various processes that share aspects of management. A distinction has traditionally been drawn between cystic and non-cystic fibrosis bronchiectasis. Cystic fibrosis (CF) bronchiectasis affects a well-defined population of patients for whom respiratory disease is the main predictor of mortality; care is provided by specialized teams, and more research and commercial activity has been undertaken than in non-CF bronchiectasis. Nevertheless, this group represents only a small percentage of all cases of bronchiectasis. Non-CF bronchiectasis, on the other hand, affects a heterogeneous population of patients with different etiologies, including cases of unknown cause, each of which has its particular characteristics [1]. Historically, this "non-CF" bronchiectasis population has been considered to be a rare disease and, therefore, specialized treatment units have been lacking, resulting in less research and commercial interest.

CF is a genetic disease found in 1:2000–3500 babies born in northern Europe and North America, with a calculated carrier frequency of 1 in 25. It is estimated that there are between 70,000 and 100,000 people with CF worldwide; however, it

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is still underdiagnosed in some countries [2] due to the variability of the diagnostic methods used, the limited availability of newborn screening, and deaths before diagnosis. Registry data suggest that the prevalence is increasing due to longer survival [3]. The estimated survival was 41.5 years in the United Kingdom (UK) in 2011 [4], whereas it is expected that children born in 2010 will live well into their 50s. In the United States (U.S.) Registry, the percentage of adult patients with CF increased from 29.2% in 1986 to 49.7% in 2013 [5]. This increase in survival means that more than 50% of CF patients are now over 18 years of age in several countries. Advances in genotyping of CFTR mutations have also contributed to the increased prevalence of the disease, as we now identify mild phenotypes that in the past remained undiagnosed [6, 7]. The impact of recently approved therapies treating the basic defect, as well as treatments to eradicate primary infection by *Pseudomonas aeruginosa*, will probably also contribute to increasing the prevalence of this disease.

The real incidence and prevalence of non-CF bronchiectasis (hereafter referred to as bronchiectasis) in general populations is not known, and it is difficult to estimate the numbers, given that both clinical and computed tomography (CT) criteria need to be met for its diagnosis. Epidemiological studies have been performed in various countries over varying periods of time, looking at sources of data (medical insurance records [8–10], hospitalization diagnosis codes [11–13], primary care data [14, 15]), diagnostic criteria, and study designs. Bronchiectasis was a common disorder in the pre-antibiotic era. The incidence in the 1950s in the Bedford region in the U.K. was estimated to be 1.3 cases per 1000 people [16], and the most common etiology was post-infection. The prevalence of a post-infective cause in developed countries has decreased dramatically—owing to the better control of tuberculosis, routine immunization in childhood, more effective antibiotics for respiratory infections, and improvement in social conditions, although it is still the most common known cause of bronchiectasis worldwide [17]. The lack of epidemiological data may have given the impression of the absence of a health problem, but fortunately some light has been shed on the subject by recent studies that show that the incidence and prevalence of bronchiectasis in adults has increased steadily over the last few decades [11, 12, 14].

Studies analyzing healthcare claims based on the International Classification of Diseases (ICD) diagnosis codes showed an estimated prevalence of 52.3 cases per 100,000 in the U.S. between 1999 and 2001 [8], and 67 cases per 100,000 in Germany in 2013 [9]. In both studies, the prevalence was higher in people over age 75 (271.8 and 228 cases per 100,000 in the U.S. and Germany, respectively). In another study in the U.S. from 2000 until 2007, the estimated prevalence in individuals older than 65 was 370 cases per 100,000 person-years, and the highest prevalence rate was found in women aged 80–84 years, at 537 per 100,000. In this same study, the prevalence of bronchiectasis was found to have increased each year by 8.7% [10]. (Table 3.1).

Data from the discharge diagnosis code register of all hospitals in Finland showed a decrease in bronchiectasis-related hospital treatment between 1972 and 1992,

Table 3.1 Prevalence of bronchiectasis in studies analyzing healthcare claims based on the International Classification of Diseases diagnosis codes

First author (ref.)	Country	Period of time	Prevalence
Weycker et al [8]	United States	1999–2001	52.3 per 100,000 adults Persons aged 18–34: 4.2 per 100,000 Persons aged ≥75: 271.8 per 100,000
Seitz et al [10]	United States	2000–2007	370 per 100,000 persons aged ≥65 years Women aged 80–84 years: 537 per 100,000
Ringshausen et al [9]	Germany	2013	67 per 100,000 persons Men aged 75–84 years: 228 per 100,000

when the diagnosis was mostly made by bronchography [13]. In contrast, later studies in the U.S. [12] and Germany [11] provided evidence of a steadily increasing prevalence of bronchiectasis-associated hospitalizations. Data from 1993 until 2006 in 12 states of the U.S. showed a significant increase in bronchiectasis-associated hospitalizations in that period, with the highest average annual increase of 5.7% taking place between 2001 and 2006. The overall annual age-adjusted hospitalization rate was 16.5 hospitalizations per 100,000 population, with the highest rate among women and people older than 60 [12]. Data from Germany between 2005 and 2011 showed an average annual age-adjusted rate for bronchiectasis of 9.4 hospitalizations per 100,000 population, which was lower than for the American population, although it needs to be taken into consideration that here only 48% of patients were above age 65, as opposed to the 70% figure found in the American study. The highest rate of hospitalizations, 39.4 per 100,000 population, was among men aged 75–84, and the most pronounced average annual increases were among women. Chronic obstructive pulmonary disease (COPD) was found to be the most frequent associated condition [11].

Recent studies using primary care data have also shown that the incidence and prevalence of bronchiectasis increases with age [14, 15]. In the U.K., its incidence and prevalence increased year by year between 2004 and 2013, with an increase in almost all age groups, but with the greatest increase in women above 70; this increased from 21.24 per 100,000 person-years in 2004 to 35.17 per 100,000 person-years in 2013, and in men from 18.2 per 100,000 person-years in 2004 to 26.92 per 100,000 person-years in 2013. The point prevalence in women increased from 350.5 per 100,000 in 2004 to 566.1 per 100,000 in 2013, and in men from 301.2 per 100,000 in 2004 to 485.5 per 100,000 in 2013. Perhaps against expectations, bronchiectasis in this industrialized country was more common in patients from a higher socioeconomic standing, as measured by the Index of Multiple Deprivation [14]. In Catalonia in 2012, a prevalence of 36.2 cases per 10,000 inhabitants, with an incidence of 4.81 per 10,000 inhabitants, was reported. Higher rates were found in women than in men; men above age 65 had the highest prevalence and incidence [15]. (Table 3.2).

Table 3.2 Incidence and prevalence of bronchiectasis in studies analyzing primary care data

First author (ref.)	Country	Period of time	Incidence	Prevalence
Quint et al [14]	United Kingdom	2004–2013	[a]Women 2004: 21.2 2013: 35.2 [a]Men 2004: 18.2 2013: 26.9	[b]Women 2004: 350.5 2013: 566.1 [b]Men 2004: 301.2 2013: 485.5
Monteagudo et al [15]	Catalonia	2012	Women 4.93 per 10,000 persons Men 4.69 per 10,000 persons	Women 39.1 per 10,000 Men 33.3 per 10,000

[a]Data are presented as incidence per 100,000 person-years
[b]Data are presented as prevalence per 100,000

Most population-based data are derived from ICD diagnosis codes, which have the limitation of not revealing whether the diagnoses have been fully established. Data from a retrospective study of 1409 participants aged 23–86 who had participated in a health screening program in 2008 in Seoul (in which they themselves made the decision to pay for a CT scan for the early detection of lung cancer), showed that 129 (9.1%) cases of bronchiectasis were identified by CT; however, respiratory symptoms were present in only 53.7% of subjects. The prevalence was higher in women and tended to increase with age. The limitations of this study were that this self-selected population may not have been representative of the general population, since patients with severe respiratory diseases and those who could not afford the cost of the CT were not included, and conventional spiral CT was performed, rather than HRCT [18].

Although a decrease in bronchiectasis might have been expected over the last decades, owing to better living conditions, better treatment of respiratory infections, and vaccination programs, studies have shown an increase in both their incidence and their prevalence. Possible reasons for this growth may be increased recognition due to the greater use of CT scans to assess patients with lung diseases [14], as well as routine study, both in diseases with a high risk of developing bronchiectasis [19] and in those associated with bronchiectasis. The condition may also be increasing due to the more frequent presence of immunosuppressive states. While a much higher number of radiologically determined cases of bronchiectasis would be found in the general population than are estimated in the studies, were it possible to perform such a study, a high proportion of these would be largely asymptomatic. The priority is—and should be—to detect bronchiectasis early in patients with diseases that have a high risk of developing the condition, as well as in patients with clinical symptoms. The clinical heterogeneity of bronchiectasis and the great number of etiologies, some of which are uncommon, justify the establishment of international registries to improve our knowledge of the epidemiology of this condition [20].

3.2 Mortality Attributable to Bronchiectasis

Bronchiectasis is a chronic and progressive condition, and there is little information available regarding mortality. The prognosis for bronchiectatic patients treated in hospital was found to be better than for that of COPD patients, but poorer than the prognosis for asthmatics in Finland at the beginning of the 1990s [21]. The average age at death is higher today than was reported in earlier studies, which may partially reflect improvements in medical therapies [22–25]. Retrospective studies have shown that the number of deaths increased by 3% per year between 2001 and 2007 in England and Wales, and that older age, male gender, a history of smoking, low socioeconomic status, and lower lung function were associated with an increased risk of mortality [25–29].

Prospective studies in single centers in various countries have shown a 4-year survival rate of between 58% in Turkey [30] and 91% in England [31] in patients with clinical bronchiectasis. In Turkey, 16.3% of the patients died over a 4-year follow-up (median age: 72), and bronchiectasis or bronchiectasis-related disorders were the cause of death in all of them. In univariate analyses, low body mass index, increased age, hypoxemia, hypercapnia, worsening dyspnea, and poorer lung function were associated with increased mortality [30]. In a British tertiary center over a 13-year period, 29.7% of patients died (median age was 60); the cause of death was respiratory in 70.4% of the patients. In addition to age and respiratory function, male gender, *P. aeruginosa* infection, and lower quality of life were all independently associated with mortality. The survival rate was 91% at 4 years, 83.5% at 8.8 years and 68.3% at 12.3 years. The prevalence of COPD was low, and 77% of the patients had never been smokers. Differences in mortality rates among the various etiologies could not be assessed because the subgroups were too small. This study did not evaluate the presence of comorbidities that can influence the death rate [31]. In a single center in Belgium, the overall mortality for newly diagnosed patients with bronchiectasis with a median follow-up of 5.18 years was 20.4%. Risk factors for lower survival were the association of COPD (an association which, in contrast to the English study, was found in 17% of patients), a greater number of affected lobes and, as in the two earlier studies, increasing age. Fifty-eight percent of deaths were due to respiratory failure, most frequently as a result of respiratory infection, and 16% were attributable to cardiovascular causes [32].

Data from a study of primary care databases in England and Wales showed that bronchiectasis is associated with markedly increased mortality. Mortality for both men and women with bronchiectasis is more than twice the mortality in the general population, independently of age differences between the two populations. The study was not able to determine whether or not the increased mortality is due to complications from coexisting illnesses, or directly attributable to bronchiectasis [14].

Two scoring systems discussed in Chap. 12, the FACED, and the Bronchiectasis Severity Index (BSI), aim to assess the severity of bronchiectasis [33, 34]. 18.8% of patients died during a 5-year follow-up in a validation study for the FACED index

[33], and 10.2% died during a 4-year follow-up to validate the BSI [34]. The most frequent cause in both studies was respiratory disease (42.9% and 51.6%, respectively) followed by cardiovascular disorders (9.1% and 22.5%). In the FACED study, age and FEV1 were found to have the greatest predictive power of mortality of the five variables that eventually comprised the score [33]. Independent predictors of mortality in the BSI study were. in addition to age and low FEV_1, lower body mass index, prior hospitalization, and three or more exacerbations in the year before the study [34].

Multiple morbidities are frequent in bronchiectasis and can negatively affect survival [35]. An increased in-hospital mortality has been recently seen in people with bronchiectasis who were hospitalized for infective exacerbations and developed acute kidney damage, which was independently associated with older age, male gender, decreased baseline kidney function, a previous history of acute kidney damage, and a diagnosis of sepsis [36].

The presence of bronchiectasis associated with other diseases, such as rheumatoid arthritis and COPD, has implications in their prognosis. Bronchiectasis in these diseases is associated with poorer survival rates in patients with rheumatoid arthritis [37, 38] and is an independent risk factor of all-cause mortality in patients with moderate-to-severe COPD [39]. In other conditions, such as inflammatory bowel diseases [40], or after renal transplantation [41], the prognostic implications of bronchiectasis have not been well established. In adult patients with bronchiectasis on the waiting list for lung transplantation, bronchiectasis with advanced lung disease was associated with significantly lower mortality risk compared to CF bronchiectasis, although separate referral and listing criteria for transplant in both populations should be considered [42].

3.3 The Economic Burden of Bronchiectasis

In the ERS Whitebook (http://www.erswhitebook.org/), the annual total cost of respiratory diseases in the EU, including the value of disability-adjusted life-years (DALYs lost), is estimated to be a minimum of €380 billion. However, the economic burden of bronchiectasis is not given. Indeed, there are only five published economic studies that provide concrete cost figures of the economic burden of bronchiectasis, two from Europe and three from the USA. A brief review of each follows.

De la Rosa et al. [43], in a retrospective cohort study, included the 456 adult bronchiectatic patients (mean age 67.2 years) cared for in six Spanish hospitals between January and December 2013. Direct healthcare costs were modelled, case-by-case, according to the respective patient's medical characteristics, taking an average unit price per hospital stay in Spain of €3783.6 in 2012 and applying the other costs by using official tariff sources and the Spanish National Drug Directory. These costs included the course of a year from maintenance treatment, exacerbations, emergency visits, and hospital admissions. Of the patients included, 56.4% suffered from mild bronchiectasis, 26.8% from moderate bronchiectasis, and 16.9% from severe bronchiectasis. The mean annual cost per patient was

€4671.9 (± €6281.1), with costs increasing steadily with severity, as documented by the FACED score. These doubled at every stage of increase in severity; patients with chronic bronchial infection by *P. aeruginosa* were the subgroup with the greatest impact on overall cost (69.1%). They had more hospitalizations than those who were not colonized, and most of their costs were due to inhalable antibiotics (€3682.4 per patient). FEV_1%, age, bronchial colonization with *P. aeruginosa*, and the number of hospital admissions, were the variables independently associated with a higher total cost in multiple regression analysis. These explained 55% of the variance in the cost; however, as a disease-unrelated average cost-figure for hospital admission (€3783.6) was used, the real cost of an admission for exacerbation was probably underestimated. On the other hand, there were 70 bronchiectasis (15.3%) patients with COPD, which presented a mean cost similar to that of the severe bronchiectasis (€7448.5 + €7934.6) patients, for whom the costs of COPD were not assessed separately; thus, the total cost of treating bronchiectasis may also have been overestimated in the study.

Sánchez-Muñoz et al [44] analyzed the Spanish National Hospital Discharge Data of all admissions for patients diagnosed with primary or secondary bronchiectasis over a period of 10 years (2004–2013). According to their findings, the mean cost per patient significantly decreased from €39610.5 in 2004 to €3515.4 in 2013 for the group with bronchiectasis as the primary diagnosis. However, for all other cases, the average cost increased from €4327.0 to €4558.6.

In the U.S., Weycker et al [8] used data obtained from more than 30 U.S. health plans between January 1, 1999 and December 31, 2001. A total of 1424 adult persons presenting with bronchiectasis (mean age: 61) in that period were identified from among the 5.6 million persons in the study database. In their prevalence study, a cohort of persons without diagnoses of bronchiectasis was randomly selected, probably at a 1:1 ratio, and matched on age, gender, geographic region, and six comorbid conditions (COPD, heart failure, diabetes mellitus, HIV, ischemic heart disease, and malignant neoplasms). Patients with bronchiectasis spent, on average, two (95% CI: 1.7–2.3) additional days in hospital, had 6.1 (95% CI: 6.0–6.1) additional outpatient encounters, and 27.2 (95% CI: 25.0–29.1) more days of antibiotic therapy than those without the disorder in 2001.The incremental total healthcare expenditures per year for bronchiectasis patients were on average US $5681 (US $4862-US $6593) higher than those compared to matched controls. Inpatient care accounted for 56%, outpatient for 16%, and drugs administered to outpatients for 18% of this difference. Suggesting that about 110,000 persons in the US undergo treatment for bronchiectasis, the authors estimated the aggregate medical-care expenditures due to bronchiectasis only at US $630 million annually.

Joish et al [45] calculated the economic burden of commercially insured incident bronchiectasis patients compared to bronchiectasis controls in the first year after diagnosis. Although the study was finally published in 2013, Medstat claims database entries from approximately 100 payers that captured all patient-level demographic data and all medical as well as pharmacy claims several years previously—namely, from January 1, 2005, until December 31, 2009—were used as proxy for the population. Bronchiectasis patients were identified using ICD-9

codes 494.0 and 494.1, and followed for 1 year (post new diagnosis). Individuals with CF or COPD (diagnosed at least 12 months prior to the first bronchiectasis -related medical event) were excluded. In a nested case-control design, a total of 27,438 control patients were matched in a 3:1 relation to the 9146 patients eligible for inclusion based on age, gender, geographic region, and type of health plan enrollment. The incremental burden of bronchiectasis was estimated for overall and respiratory-related expenditures using multivariate regression models that adjusted for baseline characteristics and healthcare resource utilization by the subjects over the 12 months prior to the first bronchiectasis diagnosis. Of note, all costs were inflation-adjusted only up to 2009 as a baseline year, using the consumer price index. A greater percentage of cases than controls had an increase from baseline to follow-up in both total (49 vs. 40%) and respiratory-related costs (57 vs. 25%), as the relative occurrence of pneumonia and influenza was more than seven times greater in the bronchiectasis patients than in the controls, and acute respiratory infections occurred twice as frequently. The average increases in overall and respiratory-related costs, after adjusting for differences in baseline characteristics, were US $2319 (95% CI: 1872–2765) and US $1607 (95% CI: 1406–1809), respectively. Surprisingly, in this study, the primary cost driver was not a higher frequency of hospitalizations, but an increase in outpatient visits of approximately 2 overall and 1.6 respiratory-related visits per patient per year, which amounted to an additional US $11,730 (95% CI: 1332–2127) and US $1253 (95% CI: 1097–1408), respectively.

Blanchette et al [46] assessed healthcare costs in the years before and after infection with *P. aeruginosa* among U.S. commercially insured bronchiectasis patients utilizing 2007–2013 PharMetrics Plus administrative claims. Newly diagnosed infection with *P. aeruginosa* resulted in an increase of four hospitalizations per patient on average, and total healthcare costs per patient in the year following *P. aeruginosa* diagnosis increased by 87% from US $36,213 to US $67,764.

Irrespective of the differences in study methodology with respect to inclusion criteria, type of matching (if any) and epidemiologic approach (prevalence vs. incident cost), all five studies show that the incremental direct cost of bronchiectasis as an entity are significant. However, indirect costs due to absenteeism from work is completely lacking, thereby clearly underestimating the economic burden from a societal perspective. Consequently, new economic studies, especially for Europe, with proper matching design and including both direct and well as indirect cost data, are urgently required.

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Clinical Aspects

4

Diego J. Maselli and Marcos I. Restrepo

4.1 Symptoms and Clinical Presentation

Bronchiectasis is a heterogeneous disease that presents a wide range of clinical manifestations from asymptomatic to massive haemoptysis and respiratory failure. With the widespread availability of chest computed tomography, clinicians encounter bronchiectasis more frequently in various degrees of severity and symptom burden, even in asymptomatic patients [1]. It remains to be established what the significance is of bronchiectatic lesions in asymptomatic patients. Additionally, in milder disease, the diagnosis relies on radiographic bronchial/arterial ratios, which may lead to an overestimation of cylindrical bronchiectasis due to small vascular calibres in certain patient populations [2]. For those patients that have symptomatic bronchiectasis, the most common symptom is cough, occurring in 82–96% of patients [3–6]. In fact, cough may be the only symptom for many years. Other common symptoms include daily sputum production, dyspnoea and chest pain (Table 4.1). The frequency and severity of symptoms are often related to the extent of the bronchiectasis and the coexistence with other respiratory or systemic diseases [5]. Sputum production may be affected by recurrent infections, the use of airway clearance devices, antibiotics and other therapies [7]. Patients often report frequent pulmonary infections, although a single severe respiratory infection may result in bronchiectasis. Haemoptysis occurs in 26–51% of the cases often presenting in mild fashion, but can result in shock or respiratory failure if it is massive [3–6].

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Table 4.1 Presenting clinical features of patients with bronchiectasis

Feature	%
Cough	96–82
Purulent sputum	87–75
Dyspnoea	72–60
Sinusitis	77–17
Fatigue	73
Recurrent fever	70
Haemoptysis	51–26
Depression	34–20
Anxiety	50–38
Chest pain	19–10
Inspiratory crackles	73–71
Wheezing	34–21
Digital clubbing	5–2

Rhinosinusitis symptoms like rhinitis, sinus discharge and congestion and recurrent sinusitis are reported in up to 77% of patients with bronchiectasis [8]. The reason for a high prevalence of these symptoms is multifactorial and is related to common pathophysiologic mechanisms such as immunosuppression, ciliary dysfunction, mucus viscosity and others. These observations have led to the development of the "one airway" concept, suggesting that upper and lower respiratory diseases may share underlying pathologic processes [9]. Sinus disease may influence outcomes in bronchiectasis. For example, patients with bronchiectasis and coexisting sinusitis have more species of different bacteria present in the sputum and more respiratory symptoms compared to patients without sinus disease [10].

Constitutional symptoms such as a fatigue, malaise, recurrent fevers and decreased exercise tolerance are frequently encountered in patients with bronchiectasis [3–6]. All the above-mentioned respiratory symptoms are the hallmark of bronchiectatic disease, but patients should also be evaluated for less known (but equally important) symptoms. It has been shown that depression and anxiety are an important aspect of the disease and these symptoms are more prevalent in patients with bronchiectasis compared to the general population [11, 12].

Similarly to asthma and COPD, bronchiectasis patients can have exacerbations that are characterized by episodes of acute deterioration in the respiratory status that goes beyond normal day-to-day variation. An exacerbation is defined as deterioration in three or more of the following six key symptoms (cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis) for at least 48 h *and* the determination by a clinician that a change in the treatment is required. During these episodes, the most common symptoms are cough (88–61%), dyspnoea (59–13%), change in the sputum colour (55–39%) and sputum volume (45–43%) (Table 4.2) [13, 14].

Physical examination abnormalities are often encountered in patients with bronchiectasis. A careful, complete physical examination is critical as it might reveal signs of the underlying aetiology (i.e. rheumatoid arthritis). The pulmonary exam usually reveals inspiratory crackles, diffuse rhonchi and a prolonged expiration due to airway obstruction and lingering sputum. Wheezing occurs in approximately one

Table 4.2 Clinical characteristics of patients with bronchiectasis during an exacerbation

Feature	%
Increased cough	88–61
Worsening dyspnoea	59–13
Increased purulence of sputum	55–39
Increased volume of sputum	45–43
Fever	33–23
Wheezing	34–33
Chest pain	18–14
Haemoptysis	16–5
Fatigue	45

third of the patients. Digital clubbing has been reported in 2–5% of adult patients with bronchiectasis, but as high as 52% in the paediatric population [3–6, 15]. In the terminal stages, respiratory failure and cor pulmonale may develop.

4.2 Lung Function

Patients with bronchiectasis often have abnormalities in pulmonary function testing. These are related to the extent of the disease and other coexisting conditions. Pulmonary function may be completely normal in patients with localized bronchiectasis on a single region of the lung or with mild disease. Patients with diffuse bronchiectasis typically present with an obstructive pattern characterized by reduced forced expiratory volume in 1 s (FEV_1) and a reduced FEV_1/forced vital capacity (FVC) ratio (Table 4.3 and Fig. 4.1). This pattern is common even in non-smokers [4]. Some patients may have areas of fibrosis or atelectasis resulting in decreased total lung capacity and often presenting with a mixed obstructive/restrictive pattern. During a bronchiectasis exacerbation, lung function transiently declines in some patients [13, 16]. However, the changes during an exacerbation may not be as pronounced as in patients with asthma, COPD or cystic fibrosis (CF) [16]. In contrast to CF, patients with non-CF bronchiectasis typically do not show improvements in lung function in response to antibiotics [17].

Change in lung function has been found to have prognostic value in bronchiectasis. A study followed patients with bronchiectasis prospectively for 2 years with daily symptom diaries and peak expiratory flow rate (PEFR) measurements [13]. In patients that had an exacerbation, the PEFR dropped on average by 10.6%, and a drop of greater than 10% was associated with greater symptom burden and a lengthy recovery [13]. Importantly, the group of patients that had an exacerbation experienced a significant decline in the PEFR before (mean of 6 days) a therapeutic intervention was required. Therefore, PEFR is an attractive tool to evaluate day-to-day changes in lung function and may be able to identify patients that will develop an exacerbation so that appropriate interventions can be initiated earlier [13].

The degree of impairment of lung function has important implications in patients with bronchiectasis. A study that followed 197 patients prospectively after baseline lung function measurements reported that lower FEV_1 measurements

Table 4.3 Pulmonary function test features of patients with bronchiectasis

Feature	%
Normal	22–38
Obstructive pattern	43–60
Restrictive pattern	7–8
Mixed obstructive/restrictive	11–24
Positive bronchodilator response	9–22
Reduced diffusion capacity (<80%))	24

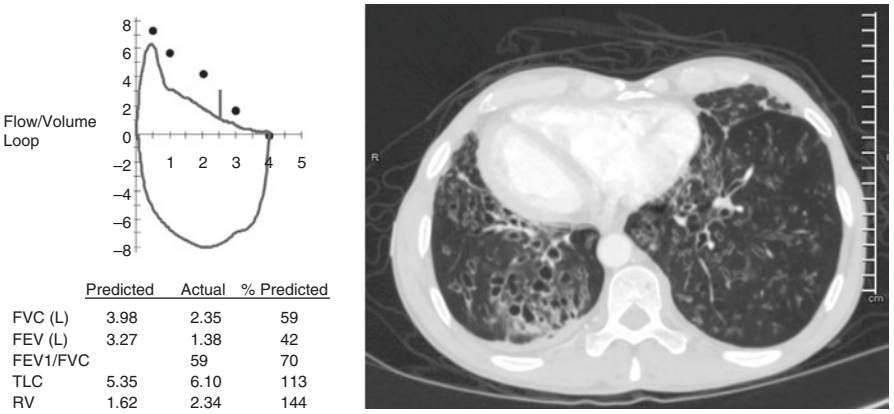

Fig. 4.1 Pulmonary function testing and chest tomography of a 57-year-old man with bronchiectasis and Kartagener syndrome. Pulmonary function testing shows severe obstruction and air trapping. Chest tomography reveals dextrocardia and advanced cystic bronchiectasis

were associated with higher number of infectious exacerbations [6]. The most common pattern observed was obstructive, and both FEV_1 and FVC were negatively correlated with imaging severity scores. Additionally, patients with a "mixed" obstructive/restrictive pattern had higher number of exacerbations compared to those with normal or an obstructive pattern [6]. Lower FEV_1 and FVC values have also been correlated with the cystic type of bronchiectasis and with the presence of *Pseudomonas aeruginosa* [5, 16, 18, 19]. Other clinical indices associated with a low FEV_1 include higher 24-h sputum volumes, more lobe involvement on imaging studies and bilateral bronchiectasis with pulmonary infiltrates [16]. Patients with CF have worse lung function compared to patients with non-CF bronchiectasis [20]. Nevertheless, lung function was not found to be different among various causes of non-CF bronchiectasis [21]. For these reasons, patients with low FEV_1 or rapidly declining lung function should be observed closely so that therapeutic interventions can be initiated promptly.

Pulmonary function testing beyond spirometry has been explored in patients with bronchiectasis. For example, impaired diffusion capacity of carbon monoxide (DL_{CO}) has been linked to greater sputum production, sputum purulence, more exacerbations, greater severity scores on imaging, positive cultures for *P. aeruginosa* and prolonged symptoms of bronchiectasis [16]. A prospective study that

followed 61 patients with bronchiectasis for a median of 7 years reported that patients of greater age and a history of smoking were associated with a faster decline in the DL_{CO} [22]. Bronchodilator response (BDR) has been reported in 8–24% of patients with bronchiectasis [3, 23]. Significant BDR is associated with poor lung function and a trend towards a lower risk of future bronchiectasis exacerbations [24]. The reasons for these findings are incompletely understood, but it is possible that differences in prescribing practices of inhaled corticosteroids might have influenced these observations. The 6-min walk distance (6MWD) has been used to assess the functional status of patients with bronchiectasis. Lower exercise tolerance has been evidenced in patients with bronchiectasis with advanced age, cystic type of bronchiectasis, high scores in symptom questionnaires and extent of the disease evidenced on imaging [24, 25].

The inflammatory profile of patients with bronchiectasis has been explored using fractional exhaled nitric oxide (FE_{NO}) with mixed results [26–29]. Kharitonov and colleagues initially described high levels of FE_{NO} in patients with bronchiectasis compared to healthy controls [26]. FE_{NO} levels were found to be normal in bronchiectasis patients who were treated with inhaled steroids. Another study showed elevated FE_{NO} levels in patients with bronchiectasis, but only in those with an asthmatic component [30]. Conversely, a study that compared patients with asthma, CF, non-CF bronchiectasis and normal subjects showed that only asthmatics had statistically significant elevations of FE_{NO} [27]. In line with these findings, two additional studies revealed normal FE_{NO} levels in patients with various aetiologies of bronchiectasis [28, 29]. Possible explanations why FE_{NO} levels are commonly not increased in patients with bronchiectasis include poor diffusion of nitric oxide across thick airway secretions, failure to activate inducible nitric oxide synthase and the heterogeneous nature of the bronchiectasis cohorts [27].

Finally, the lung clearance index, maximal mid-expiratory flow and impulse oscillometry have been used as alternate measurements of lung function in bronchiectasis. It has been shown that these tests are able to discriminate between mild, moderate and severe bronchiectasis and correlate with FEV_1 and imaging severity scores [31–33]. Although not frequently used in clinical practice, these investigations may complement assessments of severity.

For the above reasons, it is recommended that in all patients with bronchiectasis, lung function should be at least tested using spirometry [34]. Reversibility testing, lung volumes, 6MWD and DL_{CO} measurements should be obtained based on availability. The above tests can add important clinical information, particularly in severe disease, and may help identify coexisting conditions such as COPD. Additionally, both the Bronchiectasis Severity Index (BSI) and the FEV_1, age, colonization with *P. aeruginosa*, numbers of pulmonary lobes affected and dyspnoea (FACED) scores utilize FEV_1 as part of the global assessment of severity [35, 36]. Serial measurements of these investigations are encouraged, particularly in symptomatic patients and in those patients with immune deficiency and ciliary dyskinesia [34]. Moreover, these tests provide prognostic value, evaluate response to treatment and provide information regarding severity and progression of the disease.

4.3 Quality of Life

Quality of life is one of the most important aspects affected by the presence of bronchiectasis. In addition to the inherent symptoms of bronchiectasis, such as dyspnoea, cough, fatigue, haemoptysis and increased sputum production, patients have additional factors that affect their quality of life. Exacerbations, particularly if they occur frequently, also have a significant impact on the health status of patients. Even after an exacerbation has resolved with subsequent improvements in lung function and markers of inflammation, quality of life may remain poor [37]. Although some patients respond well to available pharmacological and non-pharmacological therapies, a large proportion of patients remain symptomatic and treatment regimens may create an added burden. Some of the treatments, such as nebulized therapies, take a significant amount of time to complete and may have side effects [38]. For instance, airway clearance techniques and percussion therapy may cause pain and discomfort [39]. Patients may have loss of work or school due to their disease causing further hardship. Urinary incontinency due to chronic cough can occur in as high as 47% of patients and may lead to anxiety and affect independence [40]. Additionally, increased cough or sputum production may lead to a negative perception of the patient in the community leading to isolation and can affect self-worth [41].

There are clinical makers that are associated with poor quality of life. The presence of *P. aeruginosa* in sputum has been associated to worse quality of life markers compared to other pathogens [42]. Depression and psychiatric conditions often coexist with bronchiectasis and are significant predictors of poor quality of life [11, 43]. Gastro-oesophageal reflux disease symptoms have also been linked to a decrease in quality of life [44]. The severity of bronchiectasis, as evidenced on imaging or pulmonary function, may also correlate with quality of life markers [45, 46]. For these reasons, patients with bronchiectasis should be approached in a systematic fashion with particular attention to symptoms, severity, side effects of treatment regimens and psychosocial aspects of the disease.

To evaluate quality of life, several tools and questionnaires with an emphasis in respiratory symptoms have been studied. These tools not only evaluate therapeutic efficacy in clinical trials but might provide a clinician with a clinical tool to assess treatment effect. This is particularly relevant because other markers of disease, such as FEV_1, may not always correlate with health status [47]. The St. George's Respiratory Questionnaire and the Leicester Cough Questionnaire (LCQ) have been studied and validated in multiple languages for bronchiectasis [48–51]. The former has the disadvantage that it was created for COPD and then validated for bronchiectasis. The latter has its merits but focuses on cough quality of life and doesn't encompass the whole scale of symptoms typical for bronchiectasis patients. Because of these limitations, the disease-specific Quality of Life Questionnaire-Bronchiectasis (QOL-B) was developed and validated [52]. The QOL-B is a comprehensive patient-reported outcome tool that is self-administered and approaches multiple dimensional aspects of the disease burden of

bronchiectasis [52]. It has an emphasis on patient's symptoms and activities of daily living and contains eight different scales: (1) respiratory symptoms, (2) physical, (3) role, (4) emotional and (5) social functioning, (6) vitality, (7) health perceptions and (8) treatment burden. The QOL-B was developed following the Food and Drug Administration guidelines starting with a physician consensus panel followed by patient interviews, cognitive testing and several revisions based on patient feedback. This questionnaire is publicly available and has been translated to more than 40 different languages [52, 53]. The QOL-B has been subsequently validated in different cohorts, and because of its reliability, it is considered the standard for the evaluation of the health status of patients with bronchiectasis in clinical trials and routine clinical practice [54, 55]. Although the QOL-B is a valid and strong tool, it is rather lengthy and less practical for daily practice. Recently, researchers have developed a more concise version, offering a promising fast evaluation of the quality of life of a bronchiectasis patient [56].

4.4 Natural History of the Disease

Before the widespread use of antibiotics, bronchiectasis was associated with a high degree of disability and mortality [57]. Bronchiectasis is now recognized at earlier stages because of an increase of both clinician awareness and accessibility of thoracic imaging. Additionally, with an increased understanding of the underlying mechanisms and newer treatment modalities, there has been a decrease in mortality of patients with bronchiectasis [58]. Despite these promising data, bronchiectasis still has mortality of up to 20% in 5 years and is associated with significant morbidity [59]. Factors associated with poor prognosis include advanced age, coexisting COPD and increased number of pulmonary lobes affected [59, 60]. Most patients with bronchiectasis succumb due to a respiratory associated illness [59].

The progression of the disease in patients with bronchiectasis is highly variable. This is due to the wide range of aetiologies associated with this disease resulting in multiple clinical phenotypes [61, 62]. Patients with significant radiological disease may have minimal or no symptoms [1]. Lung function declines approximately 50 mL every year in patients with bronchiectasis [63, 64]. Increased lung function decline is associated with the colonization by *P. aeruginosa*, severe exacerbations and evidence of increased systemic inflammation [35, 63]. Exacerbations may occur intermittently, and during these episodes patients have increased respiratory symptoms, worsening of lung function and poor quality of life [13]. Factors associated with poor prognosis in patients with an exacerbation include male gender, poor lung function, mechanical ventilation, history of tobacco exposure and renal insufficiency [65]. Environmental factors can also have an impact on patients with bronchiectasis. Chronic air pollution exposure has been linked to an increased risk of mortality in this patient population [66]. Ongoing prospective bronchiectasis registries will be able to provide additional information regarding the natural history of this disease [67].

4.5 Endpoints of Treatment

The objectives of the treatment of bronchiectasis are to reduce the rate of exacerbations and improve respiratory symptoms and health status/quality of life, and when an aetiology is identified, it should be treated when possible. Nevertheless, an important proportion of these patients have idiopathic bronchiectasis or aetiologies that do not have a targeted therapy yet (i.e. primary ciliary dyskinesia) [68]. Regardless of the cause, an effort should be made to disrupt the circle of bronchiectasis. This consists of an initial inflammatory insult resulting in the dilation and destruction of the bronchial walls, with subsequent impairment in the ability to clear mucous secretions, resulting in increased infection rates, augmented inflammation and ensuing in further disruption of the airways. Patients with an active infection should be treated based on microbiological data or information from previous cultures. Patients with recurrent exacerbations may benefit from chronic antibiotic use such as macrolides [69, 70]. Airway clearance techniques are employed to prevent mucus retention in the airways and have been shown to improve sputum expectoration, pulmonary function and quality of life [7]. Additionally, the clinician should focus on other aspects that may affect quality of life, such as exercise tolerance, depression, anxiety and urinary incontinence. Patients with advanced disease may have improvements in quality of life and exercise capacity after participating in pulmonary rehabilitation [71]. Surgical resection of an affected area of bronchiectasis has been effective and safe but is reserved for patients with focal disease, resistant pathogens, recurrent infections not responding to medical therapy and life-threatening haemoptysis [72].

Conclusions

Bronchiectasis has a wide range of clinical presentations. Patients with bronchiectasis have a variable degree of impairment on pulmonary function testing. Obstruction is by far the most common pattern encountered, but a restrictive pattern can occur. Poor lung function has been associated with recurrent exacerbations, cystic type of bronchiectasis, presence of *P. aeruginosa*, increased sputum production and bilateral disease. Quality of life and health status are often affected in bronchiectasis. In addition to daily respiratory symptoms and exacerbations, factors such as depression, anxiety, urinary incontinence and other social aspects may have significant consequences on the patient's well-being. The QOL-B, a disease-specific questionnaire for bronchiectasis, has been validated and is useful to objectively evaluate health status, and more questionnaires and clinical tools are being developed. For the above reasons, the care of the patient with bronchiectasis should be approached using a multidimensional strategy taking into consideration symptoms beyond the respiratory system. Therapy for bronchiectasis should target the underlying cause and focus on airway clearance and prevention of infections, without neglecting the psychosocial aspects that result from a chronic disease.

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Pathophysiology, Immunology, and Histopathology of Bronchiectasis

5

Rosario Menéndez and Oriol Sibila

5.1 Introduction

The main characteristic of bronchiectasis (BE) is permanent bronchial dilatation with chronic airway inflammation and frequent infections. There is no simple cause or mechanism to explain its pathophysiology, because bronchiectasis represents an endpoint of various causes and of a complex interplay among inflammation, immune response, and microorganisms that play a part in this chronic respiratory disease.

There are several limitations for identifying mechanisms of pathophysiology in BE: (1) the lack of animal models for replicate bronchiectasis; (2) the numerous and various pathological conditions that are implicated in its development; and (3) the limited studies investigating the pathophysiology of this condition until very recently [1].

5.1.1 Vicious Cycle

Cole in 1986 [2] proposed the first model to explain the pathogenesis of BE, calling it a "vicious cycle" hypothesis. This hypothesis suggested that after an initial infectious event that compromised mucociliary clearance, microorganisms will reproduce in the airway, provoking inflammation of and damage to the epithelium. The persistence of microorganisms that chronically infect airways would attract more inflammatory cells that release factors capable of injuring the airway and maintaining inflammation. The chronic inflammation would make microbial clearance

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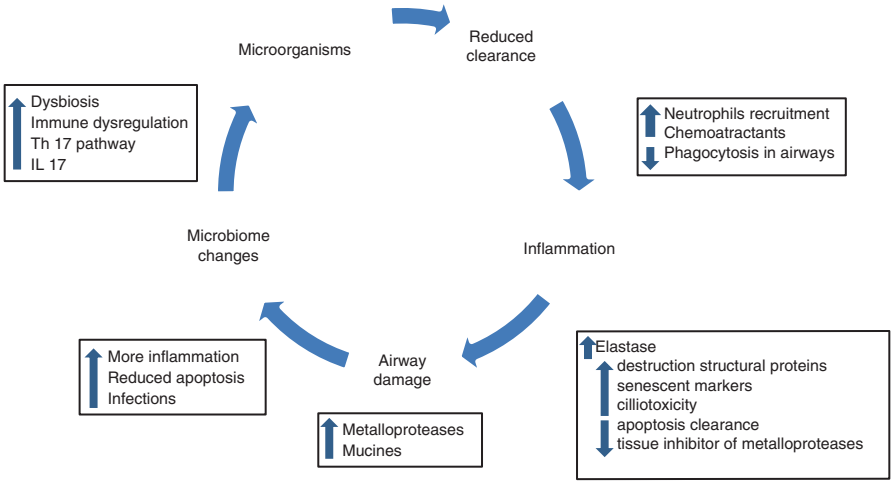

Fig. 5.1 Mechanisms involved in the vicious cycle

difficult by promoting more colonization closing—hence, the vicious cycle. Although recent investigations proved that airways are not as sterile as previously believed, the Cole hypothesis has been found to be applicable as a basis for research and for clinical investigations. In fact, some mechanisms involved in the pathogenesis of BE related to inflammation, infection persistence, and tissue damage, have now been clarified, using the "vicious cycle" as a framework. Today, it is recognized that in the pathogenesis there is an inappropriate interplay between airway host and microorganisms required to perpetuate the disease, leading to inefficient resolution of inflammation and infection, structural damage, and progression of the disease. New insights provide interesting information about the role of inflammation cells and the new concept of microbiome (Fig. 5.1).

5.2 Neutrophils

BE is considered to be a neutrophil-driven disease because these cells are crucial to its development and evolution. In the physiological host response against microorganisms, neutrophils are rapidly recruited to airways, where they degranulate their cytotoxic and immune molecules. The presence of a prominent number of neutrophils in the airway is one of the hallmarks of BE and it has been confirmed in sputum, bronchoalveolar lavage, and in bronchial biopsies in association with concomitant high levels of chemotactic molecules, such as CXCL-8 and leukotrienes LTB4 [3].

The neutrophilic airway infiltration was found also in the stable phase of the disease, and in the absence of any conventional microbiological isolate (negative culture). Nevertheless, in patients chronically infected with pathogens, the burden of the neutrophils encountered was higher [4] than in patients with negative sputum/BAL

culture. Dente et al. [5], in a cross-sectional study, examined inflammatory cells in the sputum and exhaled breath condensate of stable patients. They confirmed an increase of neutrophils in sputum that was higher in those with chronic *Pseudomonas aeruginosa*. Moreover, they correlated inflammation with severity scores (Bronchiectasis Severity Index), respiratory functional data, and the Leicester Cough Questionnaire score. In this study, they also evaluated oxidative stress determining malondialdehyde in breath condensate that was found to correlate with the number of prior exacerbations in the previous year.

5.2.1 Inflammatory Cells Recruitment and Migration to Airways (Fig. 5.2)

Neutrophils are recruited to distal airways due to the presence of high concentrations of chemoattractants—mainly IL-1b, TNF-α, IL 8 and leukotriene b4 [4]—that are contained in the airways. During migration to airways, neutrophils are activated, and there is a shedding of L-selectin; express integrins CD11/CD18 bind to ICAM-1, VCAM-1 and selectins in the endothelial cells. The role of adhesion molecules expressed on the surface of endothelial cells and leukocytes is important in BE patients because these molecules are responsible for mediating the migration of intravascular leukocytes into inflamed tissue [3]. In BE patients, the expression of CD11b/CD18 in the neutrophil surface, and L-selectin shedding, were reported to be normal, whereas in cystic fibrosis (CF), CD11b/CD18 was up-regulated and L-selectin was decreased [6]. Zheng et al. [7] have found increased serum levels of E-selectin, ICAM-1, and VCAM-1 in stable bronchiectasis patients. ICAM-1 increases, due to the raised levels of inflammatory cytokines—mainly TNFα and IL-1b—and VCAM-1 are also expressed in the presence of LPS. The increase of these adhesion molecules implies that they actively participate in transporting neutrophils to inflamed sites. Interestingly, both E-selectin and ICAM-1 levels were inversely related to forced expiratory volume in 1 s

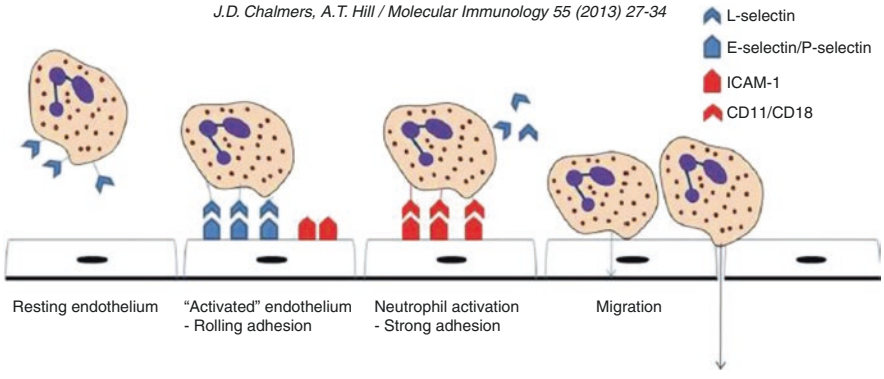

Fig. 5.2 Neutrophil recruitment to airways. From [3]

(FEV1) and positively with the number of affected lobes. The authors suggest that the source of this up-regulation of neutrophil migration could take place in the endothelium of dilated airways.

All these findings together seem to suggest that the recruitment process is rather normal, although highly activated, due to the raised levels of chemoattractants [8] capable of initiating and maintaining the process. It is worth pointing out that an increased bacterial load ($\geq 1 \times 10^7$ cfu/ml) has been associated with higher serum intercellular adhesion molecule-1, E-selectin, and vascular cell adhesion molecule-1 [9].

5.2.2 Neutrophil Activity and Phagocytosis

The ability of neutrophils to eliminate microorganisms is based on three mechanisms: (1) phagocytosis, through pattern recognition receptors; (2) degranulation of its granules: defensins (human neutrophil peptides), proteases—mainly elastases—mieloperoxidase, and lactoferrin; and (3) extruding DNA with the development of neutrophil extracellular traps (NETs) which, acting in combination with other antimicrobial proteins, enable the killing of microorganisms [10].

Although neutrophils in airways exhibited an abnormal function, it was conserved before getting airways [11]. In blood, no differences in phagocytic capacity or superoxide generation were found in idiopathic bronchiectasis when compared with controls; however, in contrast, Ruchaud-Saparagnano et al. described an enhancement of neutrophil phagocytosis and superoxide generation induced by granulocyte-macrophage colonystimulating factor (GM-CSF) [12].

Neutrophils isolated in the sputum of both CF and BE patients exhibited defective phagocytosis [13]. That deficiency was related to a higher concentration of HNP in the lung. HNP -1, −2, −3 αHNP are proteins stored in the neutrophilic granules with an antimicrobial activity; high levels of HNP could exert an inhibitory phagocytic function. Although the exact domain of HNP that determines the disturbance in phagocytosis is not known, Voglis et al. [13] have reported depressed surface Fcγ RIII, actin-filament remodeling, enhanced intracellular Ca(2+), and degranulation. These researchers suggested that HNP could be considered a potential target for novel treatments. Despite the high number of neutrophils recruited in BE airways, its diminished phagocytosis favors a scenario that leads to inefficient bacteria killing, along with increased damage by the release of its potent proteases.

5.2.3 Neutrophil Elastase

The release of proteases, especially elastase, plays a key role in the pathogenesis. Elastase that can digest phagocytized bacteria is also capable of destroying structural proteins such as elastin, fibronectin, collagen, α1-antitrypsin, and tissue inhibitors of matrix metalloproteinase [14]. Moreover, elastase is a potent secretagogue of

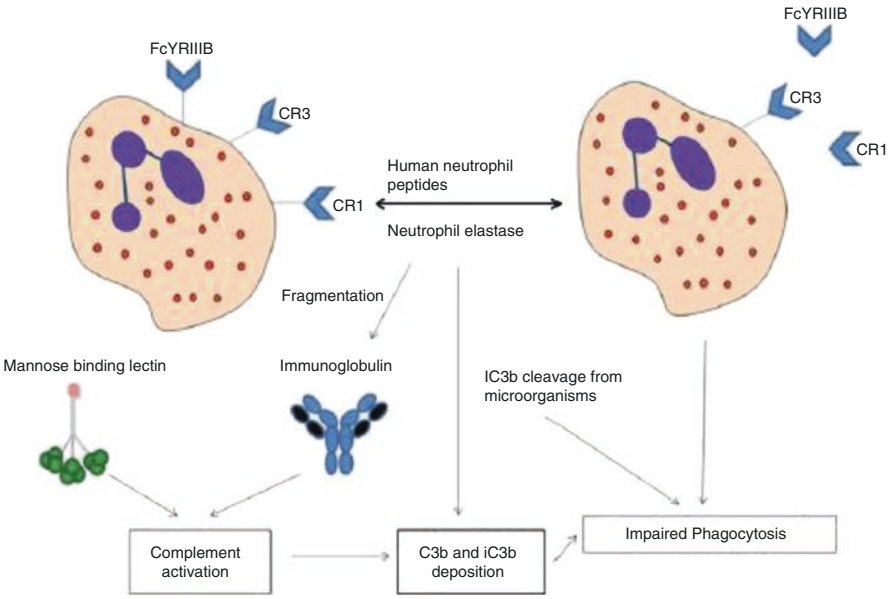

Fig. 5.3 Neutrophil phagocytic impairment. From [3]

IL-8, IL-6 release; it stimulates muc5A gene expression and granulocyte colony-stimulating factor (G-CSF). Finally, it also has cilliotoxic and cytotoxic properties that contribute to airway damage; therefore, neutrophil elastase depresses many innate defenses, facilitating *P. aeruginosa* infection [14]. There is a positive correlation between elastase levels, inflammatory markers and total gelatinolytic activity in sputum [15] with spirometric alterations and radiographic findings. In fact, elastase concentration was positively correlated with a percentage of neutrophils in a 24 h sputum volume, levels of IL-8 and TNF-α [16], and even sputum purulence.

Elastase has a considerably negative effect on phagocytosis and on the process of inflammation resolution [17]. In fact, it causes a cleavage of phosphatidylserine receptors to phagocytes, thereby disrupting the phagocytosis of apoptotic cells (Fig. 5.3). The result is a delay in apoptosis clearance. Moreover, it has been reported that a higher secondary cell necrosis and reduced number of macrophages was probably due to the concomitant proinflammatory cytokines [4], contributing to the persistence of inflammation.

Recently, elastase has also been shown to trigger the expression of senescence markers on bronchial epithelial cells [14]. In CF patients, three senescence markers –p16, gH2A.X, and phospho-Chk2—were found to be highly expressed in airway sections [18]. Elastase increased *in vitro* p16 expression and decreased CKD4 activity in CF bronchial epithelial cells [18]. In a small pilot study performed in eight BE patients, telomere-induced senescence was investigated. A significantly increased proportion of short telomeres was found without an increase in p16 expression, but

with an increase in other senescent pathways, such as p21 and TAF, and with a decrease in SIRT1 [19].

All these elastase effects are decisive for disease progression; in fact, elastase quantification has a better predictive value for lung function decline in comparison with other biomarkers *(AUROC 0.68)* [20]. This points to elastase as a potential target to contain disease, with some ongoing studies using oral inhibitors [21].

5.2.4 Metalloproteases

Matrix metalloproteinases (MMPs) are activated by neutrophil elastase and are able to degrade airway matrices, therefore playing a crucial role in extracellular matrix modelling. Their levels (except for tissue inhibitors of metalloproteinases, TIMP-1) correlated positively with sputum IL-8 and TNF-α, suggesting their relationship with neutrophil airway inflammation. Sputum MMP-8, MMP-9 and MMP-9/TIMP-1 ratio were found to be significantly increased in BE patients and positively correlated with clinical measures, including high-resolution computed tomography (HRCT) scores, spirometry, *P. aeruginosa* isolation, and the Bronchiectasis Severity Index [22].

The environment of neutrophils, elastases, cytokines, MMP, and chemoattractants leads to ongoing inflammation, along with the destruction of airways of bronchial walls. This scenario hampers bacterial elimination and contributes to maintaining airway damage. The result is persistent infection that is enhanced by the fact that microorganisms also develop mechanisms directed to evading host response, such as biofilm or hypermutation [23].

5.3 Other Cells

5.3.1 Macrophages

An increase in macrophages has been reported [4], although their specific role is not well defined. They promote neutrophil chemotaxis [24], coordinate inflammatory response by synthesis of TNF-α, IL-8, LTB4 and elastolytic enzymes, and finally eliminate apoptotic cells. The higher number of apoptotic neutrophils reported in BE patients is probably secondary to their impaired phagocytosis by macrophages due to the presence of excessive elastase [17]. Wat et al. have also found an abundance of secondary necrotic cells macrophages in sputum, and lower numbers of macrophages capable of amplifying inflammation compared levels of neutrophil apoptosis during an exacerbation [4].

5.3.2 Natural Killer (NK)

These cells accumulate in the lung parenchyma during inflammation and recruit neutrophils and T lymphocytes as part of the host response against microorganisms. Boyton and Altmann [25] have reported a functional impairment of NK that may favor the development of bronchiectasis, with increased risk of chronic bacterial infection. These events, together with excessive NK cell activation, create a highly inflammatory lung environment which, in turn, lead to the perpetuation of chronic infection.

5.4 Mucins

Mucins are the major macromolecular component of the mucus gel in health [26]. Mucus is a protective airway coating secreted in the healthy airways, composed of water, salt, and proteins. The correct balance of these components is essential for the protective function of the mucus layer. Experimental studies and clinical studies in other chronic lung diseases have suggested the crucial role that mucins play in airway defense against bacterial infections [27, 28]. In bronchiectasis, one study has evaluated the relationship among secreted mucins (MUC2, MUC 5 AC, and MUCB) and the presence of bacterial airway colonization [29]. In this study, authors included 50 stable bronchiectasis patients, showing that chronically colonized patients had higher MUC2 sputum levels compared with those without airway colonization. In addition, those patients colonized by *P. aeruginosa* showed the highest levels, and there is a correlation of MUC2 and MUC5AC levels with disease severity and neutrophil elastase activity, suggesting a role of mucins in airway defense in bronchiectasis.

5.5 Microbiome

In recent years, understanding of human lung microbiome has increased. The new technology of bacterial ribosomal RNA sequencing and related techniques have transformed our understanding of the relationship between microbial ecology and human health. Healthy airways are not sterile, and the diverse bacterial communities that exist in the oral cavity and upper airways constantly enter the lungs through micro-aspiration and are eliminated via mucociliary clearance and immune response [30–32].

Bacterial infection is central to our understanding of the pathophysiology of bronchiectasis. Traditional culture-based microbiology techniques have revealed the importance of such well-characterized pathogens as *Haemophilus influenzae* and *P. aeruginosa* [3]. However, microbiome studies have been causing an evolution in our understanding of these diseases. Previously unrecognized organisms are found in the microbiome of patients with bronchiectasis both when clinically stable and during exacerbation. Tunney et al. reported that complex polymicrobial

communities were present in the lungs of patients with bronchiectasis, including high numbers of anaerobic bacteria such as *Prevotella*, *Veillonella*. and *Actinomyces* [33]. In this study, the authors showed that microbial load and community composition—both before and after antibiotic treatment of patients with acute pulmonary exacerbations—were stable, suggesting that changes in lung microbiota composition do not account for pulmonary exacerbations.

Others studies have detected more than 140 bacterial species in the sputum and bronchoalveolar lavage of patients with bronchiectasis [34–36]. *H. influenzae*, *P. aeruginosa*, *Streptococcus pneumoniae*, *Veilonella dispar* and *Neiserria subflava* were reported to be the most common ones. Bacterial community composition was related to lung function and neutrophils count [35], suggesting that characteristics of lower airways microbiota in bronchiectasis was correlated significantly with clinical markers of disease. In addition, stratification of patients on the basis of predominant bacterial taxa (*P. aeruginosa*, *H. influenzae* and other taxa) was more clinically informative than conventional culture [34, 36]. The predominance of *P. aeruginosa*, followed by the *Veilonella* species, was the best predictor of future exacerbations frequency, while *H. influenzae*'s predominance communities had significantly fewer episodes. Furthermore, the presence of *P. aeruginosa* and *H. influenzae* was related to increased inflammatory disease in terms of C-reactive protein (CRP), IL-8, and IL-1β.

Other studies have characterized the airway microbiome following antibiotic treatment. Patients included in the BLESS trial [37] who had received long-term erythromycin treatment changed the composition of respiratory microbiota more than those who received the placebo [34, 36]. These changes were most substantial in patients with airway infections dominated by organisms other than *P. aeruginosa,* and primarily reflected reductions in the relative abundance of *H. influenzae* and increases in intrinsically macrolide-tolerant organisms. These findings suggested potentially deleterious consequences of maintenance macrolide treatment on the composition of airway microbial community, and were not detected using traditional cultures.

In some studies, researchers have begun to evaluate the role of "host response" and their relationship to the lung microbiome in various chronic lung diseases [38, 39]. The key to understanding the pathogenesis of these diseases may reside in deciphering the complex interactions between the host, pathogen, and resident microbiota during stable disease and exacerbations. In bronchiectasis, a recent study evaluated the relationships among lung microbiome and MMPs [40]. In this study, the authors evaluated the concentrations of nine MMPs and four tissue inhibitors of metalloproteinases in induced sputum from 86 bronchiectasis patients and eight healthy controls, and related their levels to airway microbiota classified as *P. aeruginosa*-dominated, *H. influenzae*-dominated, and dominated by other species. The main results were that increased MMP levels (particularly MMP-8 and MMP-1) and MMP/TIMP rations, were found in patients with bronchiectasis, compared with healthy controls. Regarding microbiomes, MMP profiles differed according to the dominant pathogen. Patients in whom *P. aeruginosa* was dominant had increased MMP-9 activity, while patients with *H. influenzae* dominance had increased

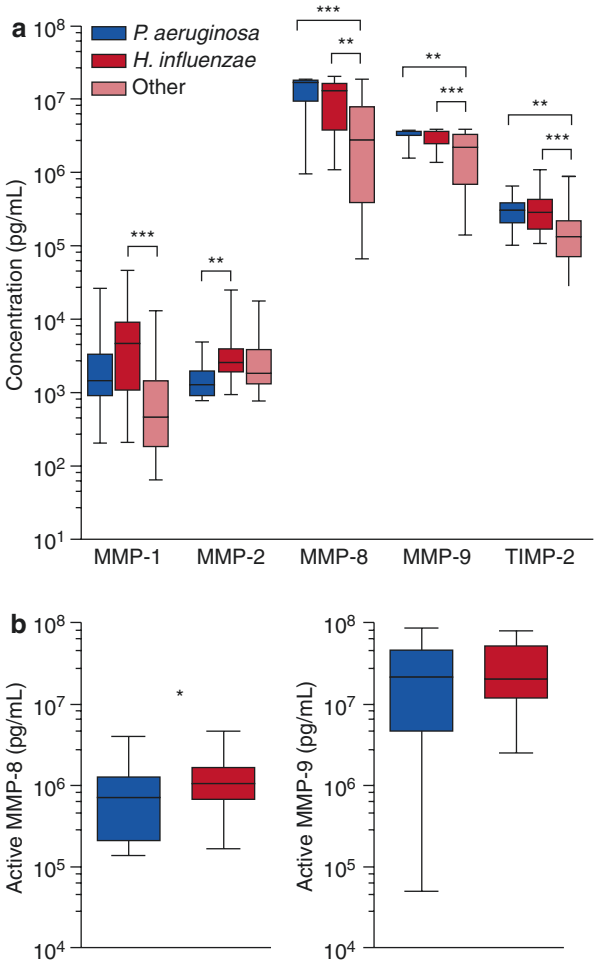

Fig. 5.4 Composition of airway microbiota and various matrix metalloproteinases. From [40]

MMP-1, MMP-2, and MMP-8 activity (Fig. 5.4). These findings suggested a possibility of differential airway remodelling according to airway microbiology.

In summary, although all of these finding may be clinically relevant, the role of lung microbiomes in the pathophysiology of bronchiectasis is not yet completely understood. Further studies concentrating on better understanding of the relationship with the host immune response are crucial for increasing our knowledge in this promising field.

5.5.1 Microbiome and Immunology

New evidence shows the role of dysbiosis and specific bacteria in modulating T-cell differentiation. Moreover, it is also possible that intestinal microbiome

drives changes in lung microbiota and lung-immune differentiation. The term "immune dysregulation" has been considered in the pathogenesis of BE, since in that disease an immune deficiency of various causes, or hyperimmune activation, may be found [41]. Several immune deficiency conditions have been associated with BE as a deficit of IgG subclasses, common variable immunodeficiency, low mannose-binding lectin levels, hyper IgE syndrome, and a defect in the transporter associated with antigen presentation [42]. On the other hand, in chronic granulomatous disease, inflammatory activation may coexist along with a component of immune deficiency.

The current state-of-the-art of lung immunology in BE is still uncertain, due to the few studies carried out on airway cells. Boyton and Altmann [25, 41] proposed a pathway for TH17 immunity. According to them, diverse microbiota species may interact with innate receptors on antigen-presenting cells favoring induction and differentiation of TH 17- CD4 cells. These cells secrete IL 17 in response to bacteria, and local IL 17 leads to neutrophilia and mucous secretions. Although the main effect of the Th 17 pathway is defending against microorganisms, it may also cause damage to the airways. A persistent TH17 activation could drive to produce ectopic lymphoid follicles with CD4 T-cells and B-cells. The activation of a TH17 pathway was studied in endobronchial biopsies and in broncoalveolar lavage. Chen et al. [43] found that Th17 cytokines—IL 17A and IL 23—were significantly higher in bronchiectasis than in control subjects, and had a higher gene expression of IL-17A, IL-1β, IL-8, and IL-23 in biopsies.

5.6 Histopathology

The main characteristic of BE is permanent irreversible dilatation of bronchial airways accompanied by wall thickening and the loss of distal narrowing. This general basic description comes from classic and older publications on lungs, from autopsies, or from surgery. In fact, there is a lack of recent pathology descriptions from a wide range of patients in distinct phases of these diseases. Traditionally, three morphologic types were described, from the less to the more severe: cylindrical, varicose, and cystic. Cylindrical BE presents thick-walled bronchi reaching the lung periphery (at 1 cm of lung), with peribronchial fibrosis and without normal tapering. The term "varicose BE" is due to the “varicose vein” aspect caused by the irregular bronchial wall. "Cystic BEs" are in general groups of cysts that may be filled with air or mucus, with a patchy distribution [44].

The thickening of bronchial airways is caused by inflammation, and normal mucosal and muscular layers are substituted by edema, ulceration, or fibrosis [45]. In later stages, polymorphonuclear transmural inflammation can be associated with micro-abscesses of airways. In proximal airways, the structural cartilage can be diminished, provoking a corresponding reduction of supportive structure. Proximal bronchi or distal bronchioles may be filled with mucus or necrotic debris, eventually forming plugs that obstruct airways. In the most advances phases, neovascular bronchial arterioles with thick walls have been described. In 1952, Whitwell [46] coined

the term "follicular bronchiectasis," due to the presence of an excessive formation of lymphoid tissue—follicles and nodes—within the walls of dilated bronchi. That finding was more frequently accompanied by an enlargement of proximal lymph nodes. The distribution and location depends on the etiology and/or cause of bronchiectasis.

Nowadays, high-resolution computed tomography (HRCT) has become the better non-invasive method for envisaging gross pathologic features in BE: morphology, distribution, extent, and severity [47]. A bronchus is considered dilated by HRCT when the luminal airway diameter is more than 1.5 times the adjacent vessel, and mucus or plugs filling the bronchus can also be observed. When small airways are affected, peripheral, irregular, short (2-4 mm) linear branching markings are noted and the term “tree-in-bud pattern” is applicable. Cysts in the bronchial wall are a feature of more destructive bronchiectasis; in more advanced cases, the grape-like cysts appear in clusters (cystic bronchiectasis).

The most modern immune-staining techniques, and the more frequent use of bronchial biopsies, have been providing detailed information with regard to the inflammatory cell types. Zheng et al. [48] in endobronchial biopsies in stable patients, have shown higher neutrophils, macrophages, and TNFα. The higher density of MMP-8 and MMP-9 positive cells in the lamina propia of airways was correlated with neutrophils, but not with macrophages [49]. Gaga et al. [24] in research on 12 patients, described inflammation with neutrophils, CD4+ T-cells, and CD68+ macrophages, increased IL-8 expression, and mucous gland hypertrophy in up to 40% of some tissue sections. The T-cells and IL-8+ cells' infiltration was lower in patients receiving corticosteroids. The presence of higher T-cell counts—CD4+, CD8+, and IL-17+ in airways—was observed in children with bronchiectasis, whether it was from cystic fibrosis or not. Tan et al. demonstrated submucosal Th17 (CD4 + IL-17+) lymphocytes in endobronchial biopsies along with IL-17+ neutrophils, γδT cells, and natural killer cells in the BE airways [50]. Recently, Chen et al. studied the gene expression of IL-17A, IL-1β, IL-8, and IL-23 in endobronchial biopsies, and Th17 pathway cytokines in bronchoalveolar lavage fluid [7], showing no differences for IL-17A gene expression. However, gene expression of IL1β and IL- 8 was significantly higher in BAL fluid, while IL-8 and IL-1α levels showed significant relationships with clinical measures and airway microbiology.

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How to Identify Causes and Predisposing Factors in Bronchiectasis

6

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6.1 Introduction

Bronchiectasis is a clinical and radiological diagnosis defining a permanent dilation of the bronchi with associated chronic cough, daily sputum production and recurrent respiratory infections leading to an increased morbidity and impaired patients' quality of life [1]. Both prevalence and incidence of bronchiectasis have not been defined yet, although recent literature reports an increase of hospitalisations due to this disease [2]. The few existing European data show a prevalence of bronchiectasis from 67 to 566 *per* 100,000, while prevalence in the USA has been estimated about 52 *per* 100,000 [3–6]. All these data have changed the earlier consideration of bronchiectasis as an orphan disease towards an increased awareness of this condition.

The clinical condition and radiological appearance of bronchiectasis are due to a variety of innate versus acquired and local versus systemic diseases resulting in heterogeneous clinical pictures. A comprehensive list of all the conditions/diseases associated with bronchiectasis is reported in Table 6.1. In light of the long list of possible aetiologies/conditions associated with bronchiectasis, an extensive and costly clinical and laboratory workup is required [7].

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Table 6.1 Conditions associated with bronchiectasis

Post-infective	Childhood respiratory infections • Pertussis • Measles • Diphtheria • Adenovirus • Tuberculosis • Swyer–James syndrome
	Others • Necrotising pneumonia • Non-tuberculosis mycobacterium • Bacterial • Viral • Funghi: blastocystis hominis infection; invasive aspergillosis; histoplasma
Immunodeficiency	Primary immune defects • Panhypogammaglobulinaemia • Agammaglobulinemia (X-linked o recessive) • Hyper-IgE syndrome • Mannose-binding protein deficiency • Qualitative antibody deficiency • IgG deficiency • IgA deficiency • Combined variable immunodeficiency • Undefined combined immunodeficiency • X-linked agammaglobulinaemia • MHC class-2 deficiency • B-cell deficiency • Chronic mucocutaneous candidiasis • Chronic granulomatous disease • Wiskott–Aldrich syndrome • Navajo poikiloderma
	Secondary immune defects • Post-chemotherapy • AntiTNF drugs • AIDS • Haematological malignancies (chronic lymphocytic leukemia, non-hodgkin lynphoma) • Transplant
Associated with lung diseases	• Asthma • COPD • Eosinophilic bronchiolitis

Table 6.1 (continued)

Congenital structural malformation	• Congenital lobar emphysema • Pulmonary artery sling • Bronchial atresia with bronchocoele • Yellow nail syndrome • Tracheobronchomalacia • Bronchomalacia • Mounier–Kuhn syndrome (Tracheobronchomegaly) • Broncho-esophageal fistula • Williams–Campbell syndrome (deficiency of cartilage formation in the 4th to 6th order segmental bronchi) • Pulmonary sequestration
Bronchial obstruction	Intrinsic • Scar stenosis • Broncholithiasis • Foreign body • Tumour
	Extrinsic • Lymphadenopathy • Tumour • Aneurysm
Genetic disease	• Pseudoxanthoma elasticum • Marfan's syndrome • Ehlers–Danlos syndrome • Alpha-1 antitrypsin deficiency
Alteration of the mucociliary escalator	• Cystic fibrosis • CFTR mutation related disease • Primary ciliary dyskinesia • Young's syndrome
Chronic sinusitis	
Inflammatory bowel diseases	• Ulcerative colitis • Crohn's disease
Hypersensitivity allergic bronchopulmonary aspergillosis (ABPA)	
Associated with connective tissue diseases	• Rheumatoid arthritis • Sjogren syndrome • Ankylosing spondylitis • Systemic sclerosis • Systemic lupus erythematosus • Relapsing polychondritis • Mixed connective tissue diseases (MCTD) • Vasculitis (Churg–Stauss; Wegener)
Sarcoidosis	
Thermal injury	
Inflammatory pneumonitis	• Aspiration (seizures, neurological disorder, cerebrovascular attacks, intoxication) • Gastroesophageal reflux • Toxic inhalation: drugs; gases (e.g: ammonia)
Diffuse panbronchiolitis	

6.2 Limitations in Understanding Aetiologies of Bronchiectasis

The understanding of aetiologies of bronchiectasis is affected by several factors.

1. The absence of an animal model along with a lack of basic science research significantly limits our knowledge of bronchiectasis pathophysiology. The association between bronchiectasis and some reported aetiologies, such as inflammatory bowel disease (IBD) and rheumatoid arthritis (RA), has been well documented by epidemiological studies, but a pathological pathway linking these two conditions is still unclear. In IBD, a close temporal relationship between curative colectomy and diagnosis of bronchiectasis is well established [8]. Even if a shift of mediators from the resected bowel to the lung due to the common embryogenic origin from the primitive foregut is postulated, but experimental data in animal model are currently lacking [9]. Furthermore, it is not known if some of the current aetiologies succeed or precede bronchiectasis development. Non-tuberculous mycobacteria (NTM), along with allergic bronchopulmonary aspergillosis (ABPA), represent a clear example of this "chicken or the egg" story. Fujita and colleagues evaluated pathological abnormalities in a case series of resected lung due to NTM disease and assumed that destruction of cartilage and smooth muscle layer as well as granuloma formation were caused by *M. avium* complex and could finally lead to bronchiectasis [10]. These findings suggest that in some cases bronchiectasis, instead of being a precursor, is likely the result of chronic NTM infection.
2. The prevalence of bronchiectasis aetiology is also difficult to determine due to small studies and the low quality of methodology used in previously reported populations. Most of the studies evaluating bronchiectasis aetiologies are single-centre retrospective studies, with no clear information on both the number and type of investigations performed. This will result in an overestimation of the proportion of patients with specific aetiologies and the wide range of idiopathic bronchiectasis which depends on the intensity of the workup performed.
3. Different definitions of the same aetiology of bronchiectasis have been reported in literature. The definition of "post-infective" as an aetiology, which accounts for the majority of known causes of bronchiectasis, is a major limitation. There is no consensus on the type/severity of previous infection which might predispose to bronchiectasis development or the acceptable time period between infection and onset of bronchiectasis symptoms. A respiratory infection could indeed be the first exacerbation of underlying but undiagnosed bronchiectasis.
4. The accuracy of identifying bronchiectasis aetiology is also affected by the well-known delay between onset of symptoms and bronchiectasis diagnosis. A landmark study by Shoemark and co-workers demonstrated a significant delay between onset of bronchiectasis symptoms (average age: 7 years) and the radiological diagnosis of bronchiectasis (average age: 49 years) [11].
5. In interpreting published data on different aetiologies of bronchiectasis, a geographical variability should be taken into account. Post-infective

aetiology, especially due to tuberculosis, greatly varies across the globe in consideration of social and economic conditions as well as access to antibiotic therapy or vaccination programmes. This aspect has been clearly highlighted in the latest systematic review published by Gao and colleagues, reporting a post-infective aetiology ranging from 18.9% to 62.5% across different geographical regions [12].

6. The association between bronchiectasis and obstructive disease, as COPD or asthma, is unexplored. COPD has a clinical and functional definition, while bronchiectasis is diagnosed by lung imaging. However, several studies have reported bronchiectasis either as a comorbidity or a co-diagnosis of COPD [13]. For patients with both diagnoses, which might be defined as an overlap syndrome, epidemiology and natural history are still unclear. Thus, different patients are currently classified in clinical practice under the same definition of bronchiectasis–COPD overlap syndrome: subjects with bronchiectasis and fixed airflow obstruction (even if they are non-smokers), those with a prior diagnosis COPD who develop bronchiectasis and even patients without an airflow obstruction, but having bronchiectasis and smoking exposure [14].

6.2.1 Prevalence of Bronchiectasis Aetiologies

More than 50 studies enrolling up to 8000 adults with bronchiectasis have investigated aetiologies of bronchiectasis as recently reviewed by Gao and co-workers [12]. Recent European data have been merged into the FRIENDS platform, analysing 1258 patients from seven European cohorts and showing an aetiology of bronchiectasis in 60% of the patients [15]. Prevalence for each aetiology is shown in Fig. 6.1. As reported in this analysis, the underlying cause could not be determined in nearly half of patients. Among the known aetiologies, post-infective seems to be the most frequent one, scoring up to 30% of cases of which post-TB is the predominant category. All the other conditions associated with bronchiectasis weighed less than 5% of cases, and immunodeficiency is the predominant aetiology. COPD may represent one of the most prevalent diseases associated with bronchiectasis, even if it has been frequently listed as an exclusion criterion in several studies.

6.2.2 Treatable Causes of Bronchiectasis

Some underlying conditions leading to bronchiectasis benefit from a specific management with a favourable impact on patients' prognosis and quality of life. Bronchiectasis may be the pulmonary manifestation of a systemic disease which might benefit from a different care in a special setting (e.g. cystic fibrosis or PCD):

1. Bronchiectasis may be the pulmonary manifestation of a hereditary disease with the need of a prompt referral to a genetic counselling and transmission risk assessment (e.g. CF or alpha$_1$-antitripsin deficiency).

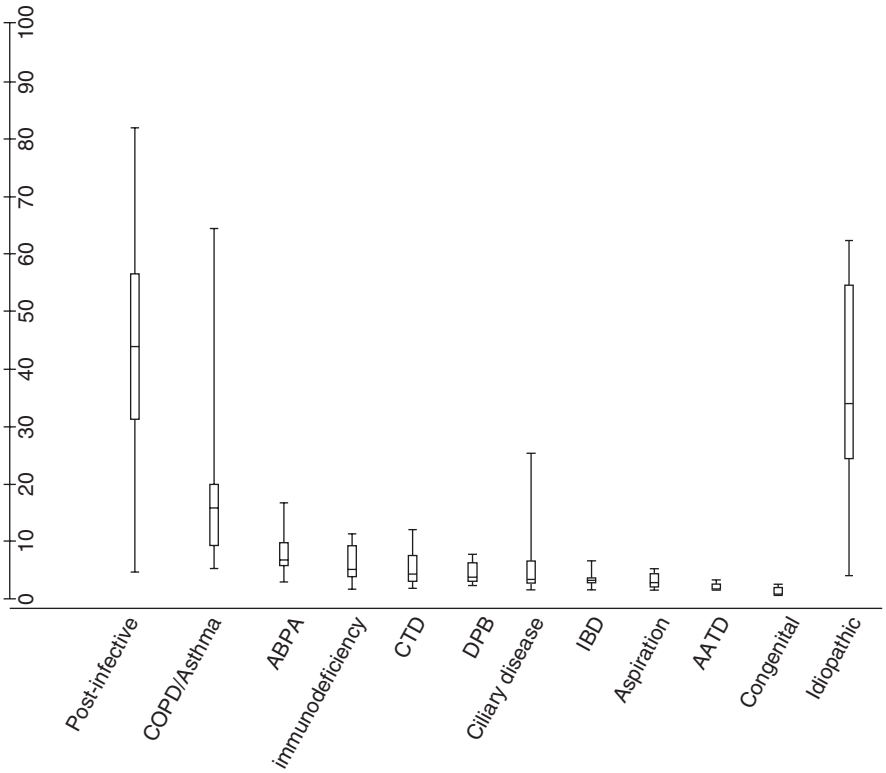

Fig. 6.1 Median prevalence of each single bronchiectasis aetiologies with 25–75 IQR and minimum and maximum data [7, 11, 15–19]

2. Bronchiectasis progression might be slowed thanks to a specific treatment of the underlying disease (CVID, NTM).
3. Bronchiectasis in the context of pulmonary (e.g. COPD) or extra-pulmonary (e.g. RA) diseases is associated to worse patients' outcomes [20, 21].

An attempt has been made by previously literature to identify the prevalence of these aetiologies. Four observational studies were identified which describe the percentage of patients (7–37%) whose management changed following investigation of aetiology [11, 15–17]. These results are consistent with those reported by Gao et al. who identified a treatable cause of bronchiectasis in 18% of patients [12]. However, a large variability in both the selection and the definitions of treatable causes exist among the evaluated studies highlighting a grey zone that should be addressed in future translational research.

6.3 Investigating the Underlying Aetiology in Bronchiectasis

Over the past few years, a number of expert groups have published recommendations on bronchiectasis care in adults, including investigations of aetiologies [22–25]. A minimum bundle of test, mostly based on expert opinion, along with specific algorithms has been reported by these guidelines in order to increase the likelihood of obtaining a diagnosis with better resource allocation, see Table 6.2. So far, none of these approaches has been validated by well-conducted prospective studies and in a large target population. Thus, no recommendations should be considered better than the others. A different approach in selecting the number and type of investigations that should be performed to identify bronchiectasis aetiology might be suggested according to the available resources and the presence of a multidisciplinary team, see Fig. 6.2. This approach is articulated in three different levels, which have been reported below with each pros/cons evaluation.

Table 6.2 Minimum bundle of investigations suggested by international guidelines

	Minimum bundle of investigations
Pulmonology Portuguese Society Bronchiectasis Study Group, 2016	• Serum AAT level or genetic analysis • Skin-prick test or IgE for *A. fumigatus* • Two measurements of sweat chloride and CFTR mutation analysis for all children and selected adults • Serum IgG, IgA and IgM and serum electrophoresis • NTM microbiology
Thoracic Society of Australia and New Zealand, 2015	• Full blood count • Serum IgG, IgA, IgM and IgE • Lower respiratory tract microbiology spirometry and lung volumes (patients aged >6 years) • Serological tests for *Aspergillus* • Sweat test in all children and selected adults
British Thoracic Society, 2010	• Full blood count and white cell differential, erythrocyte sedimentation rate or C-reactive protein, routine biochemistry • Serum IgG, IgA and IgM and serum electrophoresis • *Measurement of specific antibodies against peptide and conjugated/unconjugated polysaccharide antigens + /– response to test immunisation, if available* • Serum IgE, skin prick testing or serum IgE testing to *Aspergillus fumigatus* and *Aspergillus precipitins* • Two measurements of sweat chloride and CFTR mutation analysis for all children and selected adults • Lower respiratory tract microbiology • Pulmonary function test
Normativa SEPAR, 2008	• Lower respiratory tract microbiology • Pulmonary function test

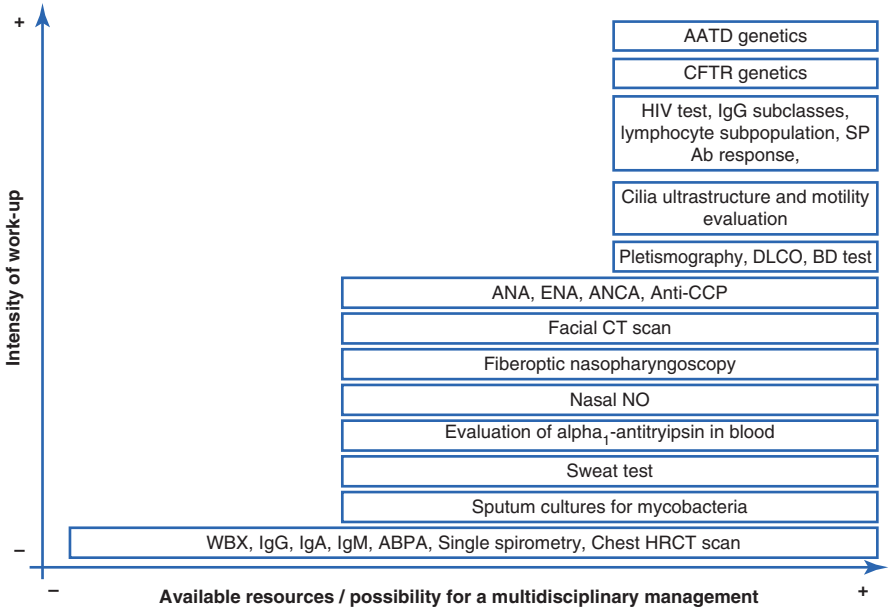

Fig. 6.2 Workup to investigate bronchiectasis suggested according to local available resources. *AATD* alpha$_1$-antitrypsin deficiency, *CFTR* cystic fibrosis transmembrane conductance regulator, *SP Ab response Streptococcus pneumoniae* antibody response, *ANA* anti-nuclear antibodies, *ENA* extractable nuclear antigens, *ANCA* anti-neutrophil cytoplasmic antibodies, *anti-CCP* anti-cyclic citrullinated peptide antibodies, *Nasal NO* nasal nitric oxide, *WBC* white blood cell, *ABPA* allergic bronchopulmonary aspergillosis

6.4 First Level

A minimum bundle of tests to be performed in all clinically significant bronchiectasis patients might include differential white cell count, serum immunoglobulins (total IgG, IgA, IgM), testing for ABPA and spirometry. Measurement of circulating white cell count and differential is crucial in all patients to identify the possible presence of lymphopaenia/lymphocytosis or neutropaenia which might suggest primary or secondary immune deficiency, or being consequence of haematological malignancy. The cost of serum immunoglobulins is generally low and results are readily available. Among them, the identification of low IgG is an important modifiable cause of bronchiectasis, and 2–8% of patients with bronchiectasis have common variable immune deficiency [11, 15–17]. Diagnosis CVID and subsequent immunoglobulin replacement treatment might significantly improve both short- and long-term outcomes. Criteria for clinical diagnosis of ABPA are very variable, but establishing ABPA diagnosis alters management [15]. The generally recommended screening tests for ABPA are total serum IgE, specific IgG to *Aspergillus* and specific IgE to *Aspergillus* [26, 27]. There are no specific criteria to diagnose ABPA in patients with established bronchiectasis. The common criteria suggested in CF have

not been validated in CF nor in bronchiectasis. Furthermore, evaluation of chest CT scan is suggested to identify specific radiological features such as congenital abnormalities or bronchial obstruction (e.g. carcinoid tumour).

The major pros of the minimum bundle approach would be (1) the detection of the most common treatable aetiologies, (2) the availability of this investigation in both primary care and secondary care hospital and (3) the relatively low cost of these examinations. On the other hand, physicians following this approach might be aware of the possibility that their patients might have other identifiable aetiologies of bronchiectasis they are missing.

6.5 Second Level

In addition to the above minimum bundle, an individualised approach might be considered:

1. In patients with either radiological or clinical features of NTM including weight loss, haemoptysis, rapid deterioration of symptoms, three sequential daily sputum cultures for mycobacterial cultures or a single BAL should be considered [28].
2. Testing for cystic fibrosis with sweat test should be considered in young adults or patients with specific clinical features such as upper lobe predominance of bronchiectasis on chest CT, culture of *P. aeruginosa* or *S. aureus*, the presence of nasal polyposis and/or chronic rhinosinusitis, recurrent pancreatitis, male primary infertility and malabsorption [22].
3. Quantitative evaluation of $alpha_1$-antitripsin in blood in the presence of emphysema.
4. Screening for primary ciliary dyskinesia with nasal nitric oxide assay should be considered for patients with several of the following features: persistent wet cough since childhood, situs anomalies, congenital cardiac defects, nasal polyposis and/or chronic rhinosinusitis, chronic middle ear disease with or without hearing loss and a history of neonatal respiratory distress or neonatal intensive care admittance [22, 29].
5. GERD should be considered in the presence of typical symptoms or patients with poorly controlled respiratory symptoms and appropriate diagnostic tests arranged [23].
6. CT scan of sinus and ENT referral in those with recurrent or persistent sinus symptoms.
7. Screening tests for connective tissue diseases by autoantibodies (ANA, ENA, ANCA, Anti-CCP) in case of clinical suspicion of CTD.

This approach might show the best cost/benefit ratio and lead physicians in identifying most of the treatable causes. This approach is dependent to individual physician experience and time consuming and will need a multidisciplinary network of specialist (ENT, gastroenterologist, etc.). There is no agreement on these approaches.

For example, the British Thoracic Society do not recommend measurement of alpha$_1$-antitrypsin routinely, and some, including some authors of this chapter, regard NTM screening as a first-line test.

6.6 Third Level

As identifying of treatable causes of bronchiectasis is a cornerstone in the management of bronchiectasis, although costly, a physician, working in a proper context, should undertake further investigations in all patients with bronchiectasis. Further investigations to consider are:

1. Biomarkers of cystic fibrosis transmembrane conductance regulator (CFTR)-mediated chloride ion transport and/or extensive CFTR gene mutation analysis are essential in the appropriate patients. The evaluation of the function of the CFTR protein by the use of NPD or rectal biopsy might support physicians' decisions in diagnosis CF.
2. Electron microscopy and analysis of ciliary function by slow-motion replay videotape recorder and a digital high-speed video camera, genetic testing for detection of PCD.
3. Alpha$_1$-antitrypsin deficiency screening by genetic analysis.
4. Further evaluation of the immune systems, including HIV test, serum IgG subclass titres, peripheral blood lymphocyte main subpopulations (including T cells, B cells and NK cells). Furthermore, some authorities recommend measuring antibody responses to *S. pneumoniae* 23 valent polysaccharide vaccine in order to identify individuals with specific polysaccharide antibody deficiency [22].
5. Complete pulmonary function tests including plethysmography and DLCO evaluation.
6. Bronchoscopy in the case of single-lobe disease to check for obstruction.

At this level the major pros would be (1) sensible reduction of idiopathic bronchiectasis in light of an increased possibility to detect not only one but also more than one aetiology of bronchiectasis and (2) the possibility to offer reliable data on aetiology prevalence to the scientific community. On the other hand, this approach is highly costly and time consuming and might be consider in specific tertiary care centres.

Conclusions

The aetiological diagnosis of bronchiectasis is a challenge and might be costly and time consuming. However, in the light of the beneficial impact on patients' outcomes, the identification of treatable conditions is warranted. We suggest a systematic approach to aetiological investigations in tertiary care and academic hospitals in order to improve our knowledge of this emerging disease.

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Immunodeficiency in Bronchiectasis

7

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7.1 Immune Deficiency and Bronchiectasis

Immune deficiencies have been identified as the cause of bronchiectasis in 6–14% [1–7] of adult and 20–34% of paediatric cohorts [8–11]. They are the third most common cause of bronchiectasis, after cystic fibrosis and postinfectious bronchiectasis, in children and adults [10, 12]. Therefore, immune deficiency should be considered in all idiopathic bronchiectasis cases, particularly if onset is in childhood [13, 14]. It is important to identify underlying immune deficiencies, as without specific treatments such as immunoglobulin replacement therapy [6, 9], these patients are at greater risk of developing progressive bronchiectasis [15], other infections and immune-mediated complications.

7.2 Immune Deficiencies Associated with Bronchiectasis

Bronchiectasis in immune-deficient patients is predominantly the consequence of chronic respiratory infection punctuated by episodes of exacerbation. Immune dysregulation and chronic inflammation may also have a role in the pathogenesis and progression of bronchiectasis in immune deficiency [16, 17]. Any defect in the

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Table 7.1 Frequency of bronchiectasis reported in various immune-deficient states

Immune-deficient state	Reported frequency of bronchiectasis
CVID	20–68% [15, 22–24]
XLA	32% (adults) [38]
SAD	18% (adults) [33]
APDS	18–60% [56–58]
STAT3 HIES	65% [62]
DOCK8 HIES	37% [63]
CGD	17% [68]
Renal transplant	2.4%
Thymoma with hypogammaglobulinaemia	10% [17]

CVID common variable immune deficiency, *XLA* X-linked agammaglobulinaemia, *SAD* specific antibody deficiency, *APDS* activated PI3-kinase delta syndrome, *STAT3* signal transducer and activator of transcription 3, *HIES* hyper-IgE syndrome, *DOCK8* dedicator of cytokinesis 8, *CGD* chronic granulomatous disease

immune system that predisposes to infection may be complicated by bronchiectasis. Table 7.1 describes the frequency of bronchiectasis reported in various immune deficiencies.

7.2.1 Primary and Secondary Immune Deficiencies

Immune deficiencies are termed primary immune deficiencies (PIDs) if aetiology is genetic or idiopathic rather than acquired or secondary to external cause. Secondary immune deficiencies (SID) are most often 'secondary' to immunosuppressive medications, chemotherapy, transplantation, HIV infection and haematological malignancies. PID that is associated with bronchiectasis development includes primary antibody deficiencies (PAD), combined immune deficiencies with T- and B-cell dysfunction and phagocytic disorders. Before a patient is diagnosed as having a PID however, secondary causes for immune deficiency should be considered and excluded.

7.2.2 Antibody Deficiencies

Defects in immunoglobulin (antibody) production are the most common immune defects identified in patients with bronchiectasis [9, 10]. Bronchiectasis is reported as a concomitant disease in 17.4% (421/2421) of patients with PAD included in the patient registry of the European Society of Immunodeficiencies (ESID) in 2016 [18]. Respiratory tract infections in these patients are most often due to encapsulated bacteria such as *Streptococcus pneumoniae* and *Haemophilus influenzae*. Immunoglobulins are important in the immune response to encapsulated bacteria as they opsonise (coat) the encapsulated bacteria activating both the complement system and phagocytes to eradicate the infection. Thus, defects in the quantity or quality of antibody production are associated with recurrent bacterial respiratory tract infections and bronchiectasis.

There are five different isotypes or classes of antibody: IgM, IgD, IgE, IgA and IgG [19]. IgM is the first antibody generated in response to pathogen, IgA is transported to mucosal surfaces, IgE is involved in immune responses to helminths and allergy and IgD is expressed by the surface of naïve mature B cells. IgG crosses the placenta, mainly in the third trimester, with the majority of serum antibody in the newborn being of maternal origin. Antibody levels in all infants fall over the first 3–6 months of life as maternally derived IgG is consumed and the infant's capacity to produce their own immunoglobulin is developed. IgG is the predominant immunoglobulin in the extracellular compartment, and patients with reduced total IgG levels (hypogammaglobulinaemia) or who have defective IgG responses to pathogens or immunisations (specific antibody deficiency) are at risk of developing recurrent chest infections and bronchiectasis. IgG can be further subdivided into subclasses, IgG1, IgG2, IgG3 and IgG4.

Primary antibody deficiencies (PAD) are the most common PID identified in adults and children affecting approximately 2.1/100,000 in the UK population [15]. They are characterised by reduced serum immunoglobulin levels and/or poor antibody responses to immunisation. Antibody deficiency can also occur as part of other PID syndromes including combined immune deficiencies. The genetic conditions underlying PAD are increasingly being recognised; however, at present, most PAD do not have an identifiable genetic aetiology. All PIDs are diagnosed in accordance with European or international diagnostic criteria based on clinical history, immune results and, where available, confirmation of known genetic mutations [20, 21]. These criteria are updated by expert panels at regular intervals reflecting the rapid development in genetics in this field.

Antibody deficiencies may be primary or secondary in aetiology. Secondary antibody deficiency may be due to medications including immunosuppressants and anticonvulsants; thymoma and haematological malignancies including myeloma, chronic lymphocytic leukaemia and non-Hodgkin's lymphoma; bone marrow transplantation; infections such as HIV, EBV, congenital rubella, CMV and *Toxoplasma gondii*; hypercatabolism of immunoglobulin; and excessive loss of immunoglobulins through nephrotic syndrome, severe burns, protein-losing enteropathy and chylous collections (lymphangiectasia) [18].

Below we describe individual PAD that may be complicated by bronchiectasis and how these are investigated. In general however if concerned that a patient with recurrent infection may have an underlying PAD, we would measure immunoglobulin levels, immunisation responses and T-cell and B-cell numbers. Assessment of immunisation responses is described further below in Section: *Determining abnormal immunisation responses and diagnosing SAD*.

7.2.3 Common Variable Immune Deficiency (CVID)

CVID is the most common significant PID representing about 20% of all PID recorded in Europe and has a minimal prevalence of 1.3/100,000 in the UK population [15]. CVID is also the most common PAD and PID to cause bronchiectasis.

CVID is characterised by recurrent infections and marked decrease of IgG and IgA with or without low IgM levels and failure to produce protective serological responses to test immunisation [20, 21]. Bronchiectasis has been reported to occur in 20–68% of individuals with CVID (see Table 7.1) [15, 22–24]. CVID is an idiopathic condition, and its onset can be at any age, though most patients present in the first two decades of life. A significant minority of patients with CVID (20–25%) develop non-infectious, immune-mediated complications such as autoimmunity, particularly autoimmune cytopenias, granuloma formation, enteropathy, polyclonal lymphoproliferation and lymphoid malignancy [25–28]. CVID patients with reduced helper T-cell (CD3+CD4+) numbers of less than 200 cells/mcl have a higher frequency of bronchiectasis and atypical infections than other CVID patients and may therefore be more appropriately classified as late-onset combined immune deficiency (LOCID) [29].

Immune Abnormalities in CVID Reduced IgG and IgA; normal or reduced IgM; poor serological response to polysaccharide pneumococcal or other immunisation; normal or reduced B cells; and normal or reduced T cells.

Genetic Investigations in CVID CVID is a diagnosis of exclusion made in cases of idiopathic reduced IgG and IgA and a history of infection. To date, in most patients with CVID, no underlying genetic cause has been identified. Targeted studies of molecules and receptors important in antibody production have identified a number of rare genetic causes of hypogammaglobulinaemia including ICOS, CD19, CD21, CD81 and BAFF receptor deficiency [30]. Increasingly, whole exome sequencing (WES) studies are being performed on cohorts of CVID patients, revealing many novel genetic findings. All WES identified novel mutations require further investigation, usually using molecular and functional techniques, to confirm if they play a plausible role in the pathogenesis of the CVID. It is anticipated that as new mutations are identified, the proportion of CVID patients who have unexplained hypogammaglobulinaemia will reduce as we increasingly identify subgroups associated with specific genetic mutations.

7.2.4 Specific Antibody Deficiency (SAD)

Specific antibody deficiency (SAD) is characterised by normal total IgG, IgA and IgM levels but failure to make an adequate antibody response to the specific antigens of infectious pathogens or immunisations [20, 21]. Polysaccharide antigen responses, such as to the pneumococcal polysaccharide immunisation (PPV), are predominantly T-cell independent, while protein antigen responses, such as to the tetanus toxoid or other protein-conjugated immunisations, are T-cell dependent. Failure to respond to polysaccharide antigens with intact protein antigen responses may be called specific polysaccharide antibody deficiency, and this implies a functional defect of B-cell function [31]. Poor polysaccharide responses are expected in infants before the age of 2 years. Patients with poor polysaccharide responses are

susceptible to encapsulated bacterial chest infections [32]. Bronchiectasis has been reported to occur in 18% of individuals with SAD (see Table 7.1) [33]. Poor immunisation responses may also be present in other PID including CVID and combined immune deficiencies.

Immune Abnormalities in SAD Normal IgG, IgA and IgM; poor serological response polysaccharide pneumococcal or other immunisations; normal B-cell and T-cell numbers.

Genetic Investigations in SAD No known genetic defects cause isolated SAD.

7.2.5 Determining Poor Immunisation Responses and Diagnosing SAD

Methods applied to assess immunisation responses vary. The most widely used approach is to compare pneumococcal specific antibody levels before and 4 weeks after administration of 23-valent polysaccharide pneumococcal immunisation (PPV-23) [34]. Anti-pneumococcal antibody assays measure either (1) the total anti-pneumococcal IgG titre or (2) multiple pneumococcal serotype-specific antibody (PSSA) levels for a variety of *Streptococcus pneumoniae* serotypes included in PPV-23. There is no universally agreed definition of a normal/poor response to pneumococcal immunisation. A fourfold increase in the total anti-pneumococcal IgG titre is regarded as normal by some, with a less than fourfold response is regarded as suboptimal and 'no response' is regarded as abnormal/poor [35]. However, if an individual has a high baseline anti-pneumococcal IgG titre, due to previous pneumococcal immunisation or infection, they may not achieve a fourfold increase post immunisation despite a normal immune system. Alternatively, a normal immunisation response can be defined as the ability to achieve an IgG titre $\geq$0.35 or 1.3 mg/mL for each *Streptococcus pneumoniae* serotype tested. With this approach, a 'normal' post-PPV-23 response is defined in those older than 6 years as 70% of the serotype-specific anti-pneumococcal IgG responses tested converting from nonprotective to protective after 4–6 weeks. In those less than 6 years, only 50% of serotypes are expected to achieve these levels [35, 36].

7.2.6 X-Linked Agammaglobulinaemia (XLA)

In XLA, formerly known as Bruton's agammaglobulinaemia, mutations in the *BTK* gene cause an X-linked condition with a severe reduction in all immunoglobulins in the blood (agammaglobulinaemia) and profoundly decreased B cells. The *BTK* gene encodes Bruton's tyrosine kinase (BTK), an intracellular tyrosine kinase critical for B-cell development in bone marrow [37]. These *BTK* gene mutations impair BTK protein function resulting in a deficiency of mature B cells and subsequent agammaglobulinaemia. Hypomorphic mutations in *BTK* can result in a partially

functioning BTK protein, and patients may have very low levels of both B cells and immunoglobulins detectable in peripheral blood. Typically, in infancy as maternal IgG disappears, boys with XLA develop severe and recurrent bacterial infections especially affecting the upper and lower airways. In a single, large study, bronchiectasis has been reported to occur in 32% of individuals with XLA (see Table 7.1) [38]. Agammaglobulinaemic patients have also been described to develop chronic enteroviral infections [39]. Less common (15%) autosomal recessive causes agammaglobulinaemia present similarly and is also due to intrinsic defects in B-cell development. They include deficiencies in pre-B-cell receptor components (μ heavy chain, λ5, Igα and Igβ) and the signalling molecules downstream of BTK, B-cell linker (BLNK) and p85α subunit of PI3 kinase (PIK) [39–41].

Immune Abnormalities in XLA Severely reduced IgG, IgA and IgM; severely reduced B cells; normal T-cell numbers. Reduced BTK protein expression on molecular testing.

Genetic Investigations in XLA BTK gene analysis.

7.2.7 IgG Subclass Deficiency

IgG subclass deficiency occurs when the total serum IgG is normal but one or more IgG subclass (IgG1–4) is deficient. Many patients with IgG subclass deficiency are asymptomatic; however, IgG2 subclass deficiency is considered more likely to be clinically significant when associated with poor immunisation responses and/or IgA deficiency. Patients with isolated IgG subclass deficiency and normal immunisation responses usually do not suffer from an increased infection rate or bronchiectasis [42, 43]. Reduced IgG subclasses may also be present in other PID including activated PI3-kinase δ syndrome.

Immune Abnormalities in IgG Subclass Deficiency Normal total IgG; reduced IgG subclass(es); normal IgM; reduced or normal IgA; normal or poor immunisation responses; normal B-cell and T-cell numbers.

Genetic Investigations in IgG Subclass Deficiency There are no known genetic defects described in this condition.

7.2.8 Combined Immune Deficiencies

In combined immune deficiencies, B-cell and T-cell function is impaired. Combined immune deficiencies are often complicated by antibody deficiency, predisposing patients to recurrent bacterial respiratory tract infections and bronchiectasis (see Table 7.1). The additional defects in T-cell-mediated immunity predispose patients to viral and opportunistic infections as well as bacterial infections. In general if

concerned that a patient with recurrent infection may have an underlying combined immune deficiency, immunoglobulin levels, T-cell and B-cell numbers and T-cell or lymphocyte function should be determined.

7.2.9 Class Switch Recombination Defects: Formerly Known as Hyper-IgM Syndromes

This group of disorders are characterised by defects in class switch recombination (CSR) resulting in reduced IgG and IgA levels and T-cell dysfunction with normal or elevated IgM levels [44]. CD40 ligand (CD40L) deficiency was the first CSR defect to be described and remains the most common. It is inherited as an X-linked disorder and is complicated by recurrent and severe bacterial and opportunistic infections, neutropenia, autoimmune disease and less frequently sclerosing cholangitis and cholangiocarcinoma [45, 46]. The related CD40 deficiency is a similar but autosomal recessive condition [47]. In addition to bacterial pneumonias, individuals with CSR defects frequently develop *P. jirovecii* pneumonia [48]. AID (activation-induced cytidine deaminase) and UNG (uracil DNA glycosylase) deficiencies are other rare autosomal recessive CSR defects which are less associated with opportunistic infections but develop more lymphadenopathy [49–52]. Patients with CSR defects are at risk of developing bronchiectasis due to recurrent or severe bacterial respiratory tract infections secondary to antibody deficiency and T-cell dysfunction. The exact prevalence of bronchiectasis in CSR deficiency is unknown but may be decreasing due to early recognition and haematopoietic stem cell transplantation in childhood.

Immune Abnormalities in CSR Defects Severely reduced IgG and IgA; normal or elevated IgM; normal B- and T-cell numbers. Reduced CD40L protein expression on activated T cells and CD40 expression on B cells.

Genetic Investigations in CSR Defects *CD40LG*, *CD40*, *AID* and *UNG* gene analysis.

7.2.10 Activated PI3K-δ Syndrome (APDS)

Phosphoinositide 3-kinase δ (PI3Kδ) is a kinase which generates phosphatidylinositol 3,4,5-trisphosphate (PIP_3). It is a heterodimer comprised of a catalytic subunit, p110δ, and a regulatory subunit, p85. PI3Kδ is expressed predominantly in leukocytes and plays an important role in their proliferation, survival and activation [53–55]. Gain-of-function mutations in *PIK3CD* and *PIK3R1*, the genes for p110δ and p85α, respectively, cause an autosomal dominant primary immune deficiency—activated PI3K-δ syndrome (APDS). Activated PI3K-δ syndrome is associated with recurrent chest and herpes infections, bronchiectasis, lymphoproliferation, hypogammaglobulinaemia and impaired immunisation responses. Studies have reported high rates of bronchiectasis, usually with paediatric onset, in APDS (see Table 7.1) [56–58].

Immune Abnormalities in APDS Normal or reduced IgG and IgA; normal or elevated IgM; normal or reduced IgG subclasses; normal or reduced B- and T-cell numbers.

Genetic Investigations in APDS *PIK3CD* and *PIK3R1* gene analysis.

7.2.11 Ataxia Telangiectasia

Ataxia telangiectasia (AT) is a disorder predominantly of the nervous system with progressive ataxia and neuropathy. It is due to mutations in *ATM* gene which has a role in controlling the cell cycle and DNA repair. AT is complicated by telangiectasia and progressive immune deficiency in some patients with recurrent sinopulmonary infections and decreased T cells and antibody levels. It is unusual for AT patients to survive beyond the second decade of life because of the development of lymphoid malignancy and/or infections.

Immune Abnormalities in AT Normal or reduced IgG and IgA; normal or elevated IgM; normal or reduced IgG subclasses; normal B-cell count; progressively decreased T-cell numbers.

Genetic Investigations in AT *ATM* gene analysis.

7.2.12 Wiskott–Aldrich Syndrome

Wiskott–Aldrich syndrome (WAS) is a X-linked immunodeficiency caused by mutations in the *WAS* gene leading to decreased T-cell responses and antibody levels. Wiskott–Aldrich syndrome protein (WASP) is a cytoskeletal protein involved in T–B-cell interactions. Patients have congenital thrombocytopenia with small platelets and, to a variable degree, recurrent bacterial and viral infections, eczema and autoimmune disease.

Immune Abnormalities in WAS Normal or reduced IgG and IgM; normal or elevated IgA; normal or reduced immunisation responses; normal B-cell count; progressively decreased T-cell numbers. Reduced WASP expression on molecular testing.

Genetic Investigations in WAS *WAS* gene analysis.

7.2.13 CTLA-4 Deficiency

Cytotoxic T lymphocyte antigen-4 (CTLA-4) is an essential negative regulator of immune responses. CTLA-4 deficiency is an autosomal dominant immune

dysregulation syndrome of incomplete penetrance (CTLA haploinsufficiency) characterised by hypogammaglobulinaemia, recurrent infections and autoimmunity including granulomatous–lymphocytic interstitial lung disease (GLILD) [59].

Immune Abnormalities in CTLA-4 Deficiency Reduced IgG and IgA; normal or reduced IgM; reduced B cells; normal T-cell numbers.

Genetic Investigations in CTLA-4 Deficiency *CTLA4* gene analysis.

7.2.14 LRBA Deficiency

LRBA (lipopolysaccharide-responsive beige-like anchor protein) deficiency is an autosomal recessive cause of childhood-onset hypogammaglobulinaemia and autoimmunity [60, 61].

Immune Abnormalities in LRBA Deficiency Reduced IgG and IgA; normal or reduced IgM; normal or reduced B-cell and T-cell numbers.

Genetic Investigations in LRBA Deficiency *LRBA* gene analysis.

7.2.15 Hyper-IgE Syndromes

Hyper-IgE syndromes (HIES) are a group of rare PID characterised by recurrent skin and lung infections, eczema and elevated serum IgE level. Over recent years underlying genetic causes have been identified in HIES. The most common cause of HIES is autosomal dominant signal transducer and activator of transcription 3 (STAT3) deficiency. Multiple forms of autosomal recessive HIES have been identified including DOCK8 (dedicator of cytokinesis 8) deficiency. Less commonly PGM3, SPINK5 and TYK2 deficiencies may cause an autosomal recessive HIES. Bronchiectasis is common in HIES with studies reporting frequencies of bronchiectasis of 65% and 37% in STAT3 deficiency and DOCK8 deficiency, respectively (see Table 7.1) [62, 63].

7.2.15.1 STAT3 Deficiency

STAT3 deficiency impairs T and B lymphocyte function, particularly effecting T-helper 17 (Th17) cells. STAT3 deficiency patients have eczema, raised IgE, eosinophilia, recurrent skin and chest infections. They develop recurrent pneumonia and pulmonary abscesses, most often due to *S. aureus* and *S. pneumoniae*, bronchiectasis, aspergillosis and characteristically pneumatoceles. The skin infections are caused by *S. aureus* and *Candida* species. Patients may also be affected by a variety of connective tissue abnormalities including coarse facial features, defective eruption of permanent teeth, hyperextensibility, scoliosis, pathological fractures and aneurysms [62, 64].

Immune Abnormalities in STAT3 Deficiency Normal IgG, IgA and IgM; normal or reduced immunisation responses; normal B-cell and T-cell numbers; elevated IgE and eosinophils.

Genetic Investigations in STAT3 Deficiency *STAT3* gene analysis.

7.2.15.2 DOCK8 Deficiency

DOCK8 is a regulatory protein involved in actin reorganisation within cells. DOCK8 deficiency causes a combined immune deficiency complicated by recurrent respiratory and skin infections and eczema with raised IgE. Compared to STAT3 deficiency, DOCK8 deficiency has an autosomal recessive inheritance, no skeletal abnormalities and significantly higher rates of viral skin infections, allergies and malignancy [65].

Immune Abnormalities in DOCK8 Deficiency Normal IgG and IgA; normal or reduced IgM; normal or reduced immunisation responses; reduced B-cell and T-cell numbers; decreased NK-cell numbers; elevated IgE and eosinophils.

Genetic Investigations in DOCK8 Deficiency *DOCK8* gene analysis.

7.2.16 Phagocytic Disorders

Chronic granulomatous diseases (CGD) are a rare group of disorders effecting 0.17/100,000 in the UK population [15] caused by X-linked or autosomal recessive mutations in genes encoding components of NADPH oxidase complex, the enzyme responsible for respiratory burst and superoxide production in phagocytes [66]. The defect in NADPH function in CGD leads to impaired killing of organisms such as *S. aureus*, *Burkholderia cepacia*, *Serratia marcescens*, *Nocardia*, and *Aspergillus* by phagocytic cells. Patients with CGD develop recurrent and severe bacterial and fungal infections predominantly abscesses, lymphadenitis and pneumonias, pneumatoceles and granulomatosis lesions [67]. In a single, large study, bronchiectasis has been reported to occur in 17% of individuals with CGD (see Table 7.1) [68].

Immune Abnormalities in CGD Normal or elevated IgG; normal IgA and IgM; normal immunisation responses; normal B-cell and T-cell numbers; absent or reduced neutrophil oxidative burst on neutrophil functional testing.

Genetic Investigations in CGD *CYBB* (gp91phox), *CYBA* (p22phox), *NCF1* (p47phox), *NCF2* (p67phox), *NCF4* (p40phox) gene analysis.

7.2.17 Mannose-Binding Lectin Deficiency

Mannose-binding lectin (MBL) is a member of the innate lectin family of pathogen-associated molecular pattern receptors that activate complement. MBL deficiency is common affecting about 5–10% of the population with most affected individuals remaining healthy and a minority complaining of an increased frequency of chest infections [69]. However, an increased risk of bronchiectasis has been reported in individuals with CVID or cystic fibrosis and MBL deficiency [70–72]. In patients with bronchiectasis, severely reduced MBL levels (<200 ng/mL) have been associated with more frequent infective exacerbations. Reduced levels of L-ficolin (ficolin-2), another complement activating member of the innate lectin family, have also been reported in bronchiectasis patients and in CVID patients who develop bronchiectasis [73, 74].

Immune Abnormalities in MBL Deficiency Normal IgG, IgA and IgM; normal immunisation responses; normal B-cell and T-cell numbers; reduced MBL level.

7.2.18 Other PID

Bronchiectasis has been described in other PID including immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) and in chronic mucocutaneous candidiasis disease (CMCD) [75, 76].

7.3 Secondary Immune Deficiencies

Secondary immune deficiencies (SID) are more common than PID [14]. The SID most frequently associated with bronchiectasis are 'secondary' to drug therapies including chemotherapy, haematological malignancies, HIV infection and transplantation [9, 10]. With the increasing use of immunomodulatory drugs for cancer and inflammatory disorders particularly in older people, the prevalence of bronchiectasis is increasing. Significant rates of bronchiectasis can develop due to SID, and in a study by Duraisingham et al., 28.2% of patient with secondary antibody deficiency developed bronchiectasis (n = 39) compared to 37.3% of primary antibody-deficient patients (n = 126) [77]. However, as SID is often a predictable complication of specific treatments and diseases, it is important to monitor at risk patient groups and intervene therapeutically with the aim of preventing the development of recurrent chest infections and bronchiectasis. In SID the most common, immunological findings are secondary hypogammaglobulinaemia and lymphopenia.

7.3.1 Drug-Induced Secondary Immune Deficiency

An increased risk of infection is a predictable side effect of many immunosuppressive medications. Medications and chemotherapeutic agents that target lymphocytes are most likely to suppress antibody production. Studies in patients with rheumatoid arthritis and inflammatory bowel disease have shown that immunosuppressants such as sulphasalazine, gold therapy, cyclophosphamide, systemic glucocorticoids and, to a lesser extent, azathioprine and methotrexate have been associated with higher rates of infection, including pneumonia, and the development of antibody deficiencies in these patient groups [78–82]. Rituximab, an anti-B-cell therapy, is used to treat severe autoimmune conditions and some haematological malignancies. Rituximab, especially with multiple treatments, has been associated with hypogammaglobulinaemia complicated by recurrent chest infections and bronchiectasis [83, 84]. Systemic glucocorticoid use, short high dose and low dose over months or years, can also induce hypogammaglobulinaemia [85]. More surprisingly, various anticonvulsants, including carbamazepine, phenytoin and valproate, have been described to induce antibody deficiency which can be complicated by respiratory tract infections [86–92].

Drug-induced immune deficiency often resolves following cessation of the implicated medication. Patients on medications known to be associated with SID should be monitored. If recurrent or severe infections are noted, we would advise patients be investigated and managed as described below.

7.3.2 Haematological Malignancies and Secondary Immune Deficiency

In haematological malignancies, such as multiple myeloma, chronic lymphocytic leukaemia and lymphoma, both the malignancy and the treatment may contribute to a secondary immune-deficient state.

Multiple myeloma is a malignant disorder of plasma cells in which abnormal monoclonal antibody is produced, and conversely normal polyclonal antibody production is often reduced. Dendritic cell, T-cell, NK-cell and B-cell dysfunction has been identified in myeloma patients [93]. Infection is the leading cause of death in patients with multiple myeloma [94, 95]. Myeloma may be complicated by infection, including pneumonia and sepsis, due to *S. pneumoniae*, *H. influenzae*, gram-negative *Bacillus* and *S. aureus* [95, 96].

Chronic lymphocytic leukaemia (CLL) is the most common leukaemia in the developed world effecting 4.1 in 100,000 individuals [97]. CLL is associated with B-cell dysfunction, hypogammaglobulinaemia and low pneumococcal antibody levels. Patients with CLL and evidence of antibody deficiency have been identified to be more likely to develop infections than individuals with CLL alone [98, 99].

Thymoma can be complicated by hypogammaglobulinaemia with reduced B cells and variable degrees of T-cell defects. Thymoma with secondary hypogammaglobulinaemia, also known as Good's syndrome, was found to be complicated by

bronchiectasis in 10% of cases on a systematic review of 152 cases [17]. Patients with Good's syndrome may also develop autoimmune diseases such as pure red cell aplasia and myasthenia gravis.

The treatments for these haematological malignancies may contribute to the immune deficiency. Older chemotherapeutic agents induced myelosuppression, while newer targeted therapies such as anti-CD20 antibodies (rituximab, ofatumumab and obinutuzumab), proteasome inhibitors (bortezomib) and kinase inhibitors (ibrutinib and idelalisib) are associated with a narrower range of B- and T-cell inhibition. Haematopoietic stem cell transplant is also associated with myelosuppression and a period of significant immunosuppression. As with other forms of drug-induced SID, once therapy ceases, immune function will usually improve over a variable period of time. However, if severe or recurrent chest infections occur during this immunosuppressed period, patients will be at risk of developing bronchiectasis.

7.3.3 Transplantation

Bronchiectasis has been described following solid organ and haematopoietic stem cell transplantation. The bronchiectasis post transplantation has been related to immunosuppressive medications and pulmonary graft-versus-host disease, bronchiolitis obliterans [100–105]. Allogeneic haematopoietic stem cell transplant is also complicated by the loss of memory T and B cells and potentially poor immune reconstitution.

In solid organ transplantation, long-term immunosuppressive therapy is often indicated to prevent allograft rejection. The development of bronchiectasis in adults and children postrenal transplantation has been related to mycophenolate therapy, specifically the development of antibody deficiency due to mycophenolate therapy [106–112]. Mycophenolate inhibits purine synthesis and severely depresses both cell-mediated and humoral immunity by inhibiting T-cell and B-cell proliferation. In paediatric heart transplant recipients, the development of bronchiectasis has been related to transplant before 4 years old and poor pneumococcal immunisation antibody responses [113, 114].

7.3.4 HIV

Untreated HIV infection is characterised by a progressive decrease in helper T-cell (CD3+CD4+) numbers. HIV infection predisposes individuals to lower respiratory tract infections with pathogens such as *S. pneumoniae*, *H. influenzae* and *Pneumocystis jirovecii* and respiratory viruses such as parainfluenza [115]. Lymphocytic interstitial pneumonitis can occur in HIV-positive individuals, though the incidence has declined with increasing access to antiretroviral therapy [116]. Bronchiectasis has been described to occur in 5–16% of children with HIV [115, 117]. The development of bronchiectasis in HIV-positive

children has been associated with lymphocytic interstitial pneumonitis, recurrent pneumonias and reduced helper T-cell (CD3+CD4+) numbers of less than 100 cells/mcl [117, 118].

7.4 Investigations

Immune deficiency is more likely to be the underlying cause of bronchiectasis if the patient has a history of recurrent chest infections and infections affecting non-pulmonary sites. PIDs are more likely in patients with childhood onset of recurrent infections, a family history of PID and other non-infectious features of the particular PID described above. SID is more likely to be the cause of bronchiectasis if the patient is currently or has previously been exposed to immunosuppressants, anticonvulsants or chemotherapeutic agents or is HIV positive, has had a haematological malignancy or previously underwent solid organ or haematopoietic stem cell transplantation.

7.4.1 Investigations We Perform in All Patients with Bronchiectasis [13, 119, 120]

Test	Looking for
Neutrophil count	Neutropenia, lymphopenia and leucocytosis
IgG, IgA and IgM levels	Antibody deficiency
Serum electrophoresis in all adult patients	Multiple myeloma
Anti-pneumococcal IgG levels, pre- and 4 weeks post polysaccharide pneumococcal immunisation	Poor polysaccharide antigen responses
HIV test	HIV infection

7.4.2 Additional Immune Tests that May Be Completed Depending on Clinical History

Neutrophil oxidative burst	Chronic granulomatosis disease
Complement function	Complement deficiency
Mannose-binding lectin level	Mannose-binding lectin deficiency
Lymphocyte subsets	Suspect PID with low B, T or NK cells
Lymphocyte function tests	Suspect PID with abnormal lymphocyte function

7.5 The Management of Bronchiectasis Secondary to Immune Deficiency

The management of bronchiectasis secondary to immune deficiency includes general bronchiectasis management measures such as airway clearance and physiotherapy, patient education, influenza immunisation, antibiotic treatment for infective

exacerbations and the consideration of prophylactic antibiotics, hypertonic saline and bronchodilators where these therapies may be of benefit. Additional specific treatment measures depend on the underlying immune deficiency identified, such as the consideration of immunoglobulin replacement therapy (IRT) in patients with antibody deficiency. It is recommended that the management and monitoring of patients with bronchiectasis and immune deficiency should be provided through a joint respiratory and clinical immunology (±paediatricians) care model with access to physiotherapy and respiratory nursing services with an expertise in bronchiectasis [13, 121]. We have followed this model for a number of years with a dedicated 'Lung Defence Clinic' in which selected patients are seen by just such a multidisciplinary and multi-professional team.

7.5.1 Immunisation

All patients with bronchiectasis secondary to immune deficiency should receive the annual inactivated influenza immunisation including patients on IRT. The seasonal variation in influenza strains means that immunoglobulin products may not have protective titres of antibody against a year's specific pandemic influenza strains. Household and close contacts of immune-deficient individuals should also be offered the annual inactivated influenza immunisation. All indicated inactivated immunisations can be administered to immune-deficient individuals though the immune response to these immunisations could be suboptimal depending on the underlying immune deficiency [122, 123].

Immunisation against the encapsulated bacteria, *S. pneumoniae*, *H. influenzae* and *Neisseria* meningococcal groups A, C, W, Y and B, is recommended in patients with complement deficiencies and patients with asplenia or splenic dysfunction due to their increased risk of bacterial meningitis and overwhelming sepsis, respectively. Antibody responses to these immunisations can be monitored and additional booster immunisations administered.

Due to safety concerns, all live, attenuated immunisations are contraindicated in patients with reduced helper (CD3+CD4+) T-cell numbers less than 200 cells/mcl or impaired T-cell function, as a component of a severe combined immune deficiency, combined immune deficiency or secondary to HIV [124, 125]. In other immunosuppressed individuals, live vaccines should only be administered after consultation with an appropriate specialist [125].

7.5.2 Antibiotic Prophylaxis

As in other forms of non-CF bronchiectasis, antibiotic prophylaxis should be considered in immune-deficient patients with bronchiectasis who have frequent infective exacerbations. Immune-deficient patients however may also be candidates for antibiotic prophylaxis due to chronic rhinosinusitis and other recurrent bacterial infections [126]. Antibiotic prophylaxis is also advised in patients with complement deficiencies or splenic dysfunction. In patients with combined immune deficiencies,

prophylactic co-trimoxazole, antivirals and antifungals may also be indicated to prevent atypical and nonbacterial infections.

7.5.3 Immunoglobulin Replacement Therapy (IRT)

Immunoglobulin replacement therapy (IRT) consists of long-term, regular infusions of pooled donor IgG (normal immunoglobulin) and should be considered in all patients with primary and secondary antibody deficiency and bronchiectasis to reduce their infection frequency. In some primary antibody deficiencies, such as XLA and CVID, IRT is an essential part of the standard of care, and all patients should be commenced on IRT [127]. In addition, all IgG-deficient or specific antibody-deficient (primary or secondary) patients with recurrent chest infections or infective exacerbations of bronchiectasis despite a trial of antibiotic prophylaxis should be considered for IRT [77]. A recent survey of immunologists found that objective evidence of recurrent chest infections (number of proven infections, pharmacy-confirmed prescriptions, etc.) was the most important factor in the decision to commence IRT in antibody-deficient individuals [128].

IRT can be given by intravenous (IVIG) or subcutaneous (SCIG) infusion with the interval between doses varying from a few days to every 3 weeks, depending on immunoglobulin product used and individual patient need and preference. IRT can be administered in the hospital day ward setting or as home therapy. Home therapy IRT is usually self-administered by the patient or by their relatives after a period of training [129].

Our current practice is that IRT is usually commenced at a dose of 0.4 g/kg/month in patients without bronchiectasis and at a higher dose of 0.6 g/kg/month in antibody-deficient patients with bronchiectasis [128, 130, 131]. Patient response to immunoglobulin and clinical requirement to increase immunoglobulin dose is determined by monitoring the patient's frequency of infection in conjunction with their trough (predose) or steady state IgG levels [132, 133]. Studies have suggested that the use of higher doses of immunoglobulins to maintain IgG troughs at up to 10 g/L may reduce frequency of overall infection and pneumonia in particular [133–135].

Normal immunoglobulin is derived from blood donations and is thus a finite resource. Increasingly normal immunoglobulin is administered in the treatment of other medical conditions. To ensure the immunoglobulin supply of patients with PID on long-term IRT in times of storage policies for prioritising demand, such as the Department of Health, UK, *Guidelines for Immunoglobulin Use* (update 2011), place PID as the highest priority indication for IRT [136]. SID is a 'blue' indication which means that IRT is usually made available unless there is a shortage in supply.

7.5.4 Other Treatments for PID

Allogeneic haematopoietic stem cell transplantation (HSCT) is a potentially curative, early treatment option for many combined and all severe PIDs including severe combined immune deficiency (SCID), CGD, CSR defects, APDS, DOCK8

deficiency and LRBA deficiency [44, 57, 61, 65–67]. Various studies have supported gene therapy as a potential curative treatment alternative to HSCT in SCID, CGD and WAS [137–139]. In patients with less severe phenotypes of combined immune deficiency or who have been deemed unsuitable for HSCT, other interventions such as long-term antimicrobial prophylaxis and IRT may be appropriate [57, 61, 62, 66, 67]. In CGD, adjuvant INF-gamma subcutaneous therapy may improve neutrophil and monocyte function [66, 67].

7.6 Long-Term Monitoring

In patients with bronchiectasis and immune deficiency, we aim to maintain or improve their lung function, prevent future infections and infective exacerbations in bronchiectasis, improve quality of life and ensure the normal growth and development in children [13]. We believe that these aims are most effectively achieved through specialist clinics with respiratory medicine, clinical immunology, physiotherapy and respiratory nursing and in children paediatric, involvement, as is our practice [13].

The appropriate monitoring of lung function for bronchiectasis progression is debated. Due to the risk of asymptomatic progression of bronchiectasis, it has been suggested HRCT and spirometry should be periodically performed. *Pasteur* et al. in the BTS guideline for non-CF bronchiectasis recommended the measurement of FEV1 and FVC at least four times each year in bronchiectasis patients with immune deficiency [13, 126].

7.7 Outcomes

Patients with immune deficiency and bronchiectasis have greater morbidity and mortality outcomes than those who do not develop bronchiectasis [25]. Two large studies showed that respiratory failure from chronic lung disease has historically been a major cause of death in CVID [140, 141]. Due to these associated poor outcomes, it is crucial to identify immune deficiency promptly and intervene to prevent the development and progression of bronchiectasis. A delay in the diagnosis or recognition of immune deficiency has been associated with the development of bronchiectasis in CVID patients in some, but not all, cohorts [25, 77, 142].

Conclusions

- Immune deficiency is an important cause of bronchiectasis that should be considered and investigated for in all cases of idiopathic bronchiectasis.
- The identification of an underlying immune deficiency in bronchiectasis may indicate additional therapeutic interventions.
- A delay in recognising an underlying immune deficiency in bronchiectasis may result in otherwise preventable recurrent infectious exacerbations and bronchiectasis progression as well as other infective complications.

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Chronic Rhinosinusitis and Bronchiectasis

8

Anna Nogués Sabaté and José María Guilemany Toste

8.1 Introduction

In respiratory physiology, the nose is an organ of great functional importance that contributes 50% of the resistances to airflow. Diseases of the upper airway require, in many cases, multidisciplinary care because it is next to the orbit and the skull base. In recent years, it has been demonstrated that bronchopulmonary pathologies are usually associated with sinonasal pathology, thus creating the concept of rhinobronchitis [1] and "one airway, one disease." The most studied example is the relationship between rhinitis and asthma [2, 3]; recently, it has been found that COPD is also associated with a high prevalence of chronic rhinosinusitis (CRS) [4]. The nose has the function of conditioning the air we breathe by heating, humidifying, and filtering it. The olfactory function is exerted by the first cranial nerve whose branches penetrate the roof of the nasal cavity through the cribriform plate of the ethmoid bone. The nose participates in the immune defense mechanism by creating a physical barrier (mucus, cilia) to the passage of microorganisms to the airway and an immunological organ. Finally, the nose has a function in phonating, modulating, and giving resonance to the voice.

8.2 Differences and Similarities Between Nasal and Bronchial Respiratory Mucosa

The nasal and bronchial mucosas have a similar structure. The squamous epithelium found in the nasal valve is transformed caudally in the nose into pseudostratified ciliated columnar respiratory epithelium. In the nose, this epithelium contains ciliated

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cells, non-ciliated cells, basal cells, and goblet cells. In contrast to the lower airways, the upper respiratory epithelium does not contain Clara cells, brush cells, and serous cells [5]. The basement membrane in the respiratory epithelium is composed of type IV collagen, proteoglycans, laminin, and fibronectin. Below spreads a layer of the *lamina reticularis*; this is diffusely thickened in asthmatic patients [6]. Focal thickening of this membrane is observed in patients with bronchiectasis, tuberculosis, and CRS [7]. In patients with rhinitis, no changes have been detected at this level [8].

The submucosa contains glands, blood vessels, nerves, extravascular cells, and extracellular matrix. One major difference between upper and lower airways is that only lower airways contain a layer of smooth muscle in the submucosa [5].

Glands and vessels predominate in the nose. Apart from arterial vessels, the nasal vasculature consists of capillary vessels, arteriovenous shunts, sinusoids, and venous vessels. These veins contain smooth muscle. Venous contraction results in expansion of sinusoids, which increases the size of the turbinate (erectile tissue) and in nasal air flow. In contrast, changes in flow resistance in the bronchi are caused by contraction of the smooth muscle.

The mucociliary apparatus throughout the airways is formed by numerous cilia that emerge from the surface of pseudostratified columnar epithelial cells. Each cell contains about 200–300 cilia that beat synchronously in a frequency of about 500 beats per minute [9]. An alteration in ciliary function can lead to malfunction in the mucous of secretions and predisposes to local infections. In primary ciliary dyskinesia (PCD), it can contribute to the development of bronchiectasis in this part of the respiratory tract [10].

8.3 Chronic Rhinosinusitis

CRS is defined according to EP^{3}OS consensus [11] as a sinonasal inflammation that lasts for more than 12 weeks and has the presence of two or more symptoms, one of which should be nasal congestion/obstruction/blockage or anterior/posterior nasal drip. The other symptoms can be facial pain or pressure and reduction or loss of smell. CSR with polyps is considered as a subgroup of CRS.

The diagnosis is made by the clinical history of symptoms, nasal endoscopy, and computerized tomography. To improve the pharmacological management, the anamnesis features consistent with allergy symptoms, such as eyes and nose itching, should be searched for.

The histopathology of CRS suggests that it is a diffuse inflammation of the mucosa with infiltration of neutrophils, eosinophils, mast cells, and basophils [12]. The nasal mucosa in CRS is characterized by a thickened basement membrane, goblet cell hyperplasia, subepithelial edema, and inflammatory cell infiltration.

The treatment of CRS is conservative, with intranasal corticosteroids, nasal lavage, and, in moderate or severe cases, treatment with long-term macrolide regimen [13]. Treatment with intranasal corticosteroids is the cornerstone of therapy. Intranasal corticosteroid treatment was found to be effective in preventing and suppressing inflammation at the mucosal level, and in patients with nasal polyps, nasal corticosteroid treatment was found to improve symptoms of nasal obstruction,

rhinorrhea, and sneezing [11]. Treatment with nasal corticosteroids is prolonged, and stopping treatment results in reappearance of symptoms. The effect of topical treatment on olfactory recovery is limited; however, administration of systemic corticosteroids allows the recovery of olfaction during the treatment [14].

Functional endoscopic sinonasal surgery (FESS) is reserved for those patients who do not respond to medical treatment. The FESS helps the response to treatment by enlarging the *ostia* to facilitate the secretion drainage from the paranasal sinuses to the nasal cavity. It should be kept in mind that it is not a curative treatment and up to 10% of patients require surgical revision 3 years after the first surgery [15].

8.4 Prevalence of Sinonasal Pathology in Patients with Bronchiectasis

The concept of "unified airway" explained above is widely studied in rhinitis and asthma, but there are few studies that correlate bronchiectasis and CRS. Our groups have examined the prevalence of sinonasal pathology in patients with stable bronchiectasis, basing the diagnosis of CRS on sinus CT and nasal endoscopy to reach the diagnosis [16]. The most frequent symptoms of CRS in patients with bronchiectasis were found to be anterior rhinorrhea, posterior rhinorrhea, and nasal obstruction, findings that are in agreement with the symptoms most frequently found in patients with CRS according to EP^{3}OS criteria [11]. Seventy-seven percent of bronchiectasis patients had CRS, while 25% had mild to moderate nasal polyposis. Patients with nasal polyposis were diagnosed with bronchiectasis at a younger age (more than 10-year difference) than patients without nasal pathology [16]. In asthmatic patients with CRS, the ethmoidal sinus is the most commonly affected [17], whereas in patients with both bronchiectasis and CRS, the maxillary sinuses, ethmoidal sinuses, and the ostiomeatal complex are usually affected.

It may be assumed that postinfectious, rather than "idiopathic," bronchiectasis may not be associated with CRS, due to a more focal rather than diffuse mechanism of injury. Indeed, Shoemark et al. [18] have found that bronchiectasis patients with postinfective etiology have a 50% incidence of CRS, whereas in "idiopathic" bronchiectasis, 84% have CRS ($P < 0.01$). Other studies from our groups have not found this association [16].

Patients with bronchiectasis should be referred to an otolaryngologist when presenting sinonasal symptomatology according to EP^{3}OS criteria that suggest chronic rhinosinusitis [11]. The CRS's treatment does not differ between those patients with CRS alone and those with bronchiectasis and CRS.

8.5 Bronchiectasis Severity in Relation to CSR

It is well established that patients with severe asthma have a high prevalence of sinonasal symptoms and vice versa; in fact, 53–55% of patients with nasal polyposis present bronchial hyperreactivity, whereas in the population the percentage drops to 12–14% [19].

In our studies we have observed that patients with bronchiectasis and CRS, with or without polyps, had a significantly higher bronchiectasis score on CT compared with those without CRS [16]. Between the different explanations for this finding, one option could be that CRS is a marker of activity in bronchiectasis patients.

8.6 NO as an Inflammatory Marker

In the upper airway, nitric oxide (NO) is continuously being produced by the maxillary sinus; patients with allergic rhinitis present higher levels of nasal NO [20], and for this reason, it has been proposed to be an inflammatory marker; however, in patients with nasal polyposis, nasal NO decreases proportional to the degree of occupancy, probably due to the mass effect of the polyps that obstructs the drainage of the maxillary sinus [21, 22]. Low NO is also found in PCD [23].

8.7 Impact of Bronchiectasis and CSR on Quality of Life

Our groups [24, 25] were the first to assess the effect on general quality of life (QoL) in patients with bronchiectasis and CSR using the SF-36 test. This study showed that in all domains of the test, patients with bronchiectasis and CSR were more severe than patients with bronchiectasis without CRS. Women presented worse QoL than men, a finding that was also found among asthmatic patients [26]. Patients with mild-moderate nasal polyposis (Lildholt score <1.5) had increased nasal obstruction and increased loss of smell but did not present worse quality of life in comparison with general population [24].

The SNOT-20 test, which evaluates the patient-reported measure of outcome in sinonasal disorders, showed that patients with bronchiectasis and CSR had a higher score in the test than those with bronchiectasis without CSR. No difference was observed between CRS with or without NP, but it should be taken into account that this test does not analyze nasal obstruction or olfaction, factors that may influence QoL [25].

The SGRQ test is frequently used to assess the QoL in patients with bronchiectasis, asthma, and COPD or α1-antitrypsin deficiency. Through this test it has been demonstrated that colonized patients have worse quality of life than those that aren't colonized [26]. Although there was no correlation between SNOT-20 and SGRQ in patients with COPD and nasal symptoms, there is a correlation between SNOT-20, SGRQ, and SF-36 in patients with bronchiectasis, associating the intensity of nasal symptoms with worsening QoL in the tests [27].

8.8 Importance of Smell in Patients with Bronchiectasis

CRS with or without nasal polyps is the main cause of a partial or total loss of smell in patients with bronchiectasis. The sinonasal CT scan and the nasal symptoms are sufficient for the diagnosis of CRS, but to identify the presence of

nasal polyps, nasal endoscopy is mandatory. In clinical practice, the sinonasal involvement of many patients with asthma or bronchiectasis is not addressed. Thus, an alert symptom like "the loss of smell" may raise the suspicion of concomitant CRS, leading to a referral to an ENT specialist. Proper management of CRS may prevent bronchiectasis exacerbations, in addition to improving upper airway symptoms. Also, it is of essential importance to create multidisciplinary units (with the collaboration of respiratory physicians, allergologists, and ENT specialists) to improve the global management, care, and follow-up of these patients [28, 29].

Conclusions

According to the concept of "one airway, one disease," it is confirmed that the association goes beyond asthma and chronic obstructive pulmonary diseases; many patients affected by bronchiectasis present sinonasal involvement.

The high prevalence of sinonasal pathology in bronchiectasis patients leads us to suggest that an otolaryngology referral is necessary in patients with BQ to evaluate CRS, and, conversely, patients with CRS should be studied for concomitant lower airway diseases such as asthma, COPD, and bronchiectasis. Studies suggest that CRS with or without polyps has a significant impact on the quality of life of bronchiectasis patients. Future studies will require further studies to better understand the association of the lower and upper airway in patients with bronchiectasis.

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COPD and Bronchiectasis

9

Miguel Angel Martínez-Garcia and Katerina Dimakou

9.1 Introduction

Chronic obstructive pulmonary disease (COPD) and bronchiectasis are two of the most common chronic inflammatory diseases of the airways [1, 2]. They share a similar clinical-functional picture, and this often leads to mistaken diagnoses [3]; they also share a similar inflammatory profile, dominated by neutrophils [4]. Nevertheless, the two diseases are fundamentally different in terms of their prognosis and therapeutic management [5, 6]. Over and above the fact that the two diseases could appear by chance in a single patient, the relationship between COPD and bronchiectasis is a complex one from both angles. On the one hand, the prevalence of bronchiectasis seems to increase in COPD patients (particularly in the latter's most severe forms) [7, 8]; on the other, an increasing presence of COPD can be seen in the etiological tables for bronchiectasis [9, 10]. So far, however, no study has demonstrated any causal relationship between the two diseases. Furthermore, it has been noted that patients with alpha-1 antitrypsin deficiency (a rare form of COPD characterized by the presence of panacinar emphysema, typically found in smokers), presents a high prevalence of bronchiectasis [11, 12]. Nevertheless, bronchiectasis of an unknown cause in COPD patients seems to constitute a special group or clinical phenotype with a more severe clinical-functional picture, a greater number of exacerbations, and even, according to some authors, a poorer prognosis [13–15]. One critically important aspect is the special management required by patients with both COPD and bronchiectasis since, as reflected in the international guidelines for both diseases [5, 6], each must be treated individually (and the scientific evidence shows that the same treatment can have markedly different effects on COPD and

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bronchiectasis). This chapter collates and discusses the literature to date on this complex relationship, in terms of epidemiology and the impact of bronchiectasis on patients with classical COPD, a predominance of emphysema, or an alpha-1 antitrypsin deficiency (α1-ATD). It also considers the possible therapeutic implications of this association, as well as hypotheses on a causal relationship between the two diseases and the most suitable approaches for future research aimed at expanding the scientific evidence on this subject.

9.2 Diagnostic Errors

One of the main reasons for the under-diagnosis of bronchiectasis may be the fact that it can be confused with other diseases of the airway. Such diagnostic errors usually occur because bronchiectasis tends to present a clinical-functional pattern similar to that of COPD (and, to a lesser extent, asthma). Therefore, it is common for a physician to suspect the presence of COPD in a smoker with airway obstruction, or that of asthma in women with sibilant wheezing, without including in the differential diagnosis the possible presence of bronchiectasis (whether associated with COPD or asthma or not). This situation is largely responsible for frequent and significant delays in the diagnosis of bronchiectasis. In this respect, O'Brien et al. [3] published a study that concluded that 32 of the 108 (29.6%) patients sent to a specialist for a suspected diagnosis of COPD presented normal spirometric values (incompatible with this diagnosis), and that in an HRCT, 11 of these (34.4%) presented bronchiectasis capable of explaining their symptoms. However, as the authors themselves recognized, these symptoms were indistinguishable from those found in patients with COPD. On the basis of these findings, O'Brien et al. emphasized that the possibility of bronchiectasis needs to be taken into account if a differential diagnosis is to be accurate (particularly in smokers with an increased production of sputum).

9.3 Prevalence of Bronchiectasis in COPD Patients

The real prevalence of bronchiectasis in COPD patients is not known. According to the results of various studies that directly or indirectly provide data on this subject, the prevalence ranges from 4 to 72% [3, 16–31]. There are several possible explanations for this huge discrepancy. Firstly, the results depend on the selection criteria used for the COPD patients included in the studies (selection bias), as sometimes only patients in a period of exacerbation were included [3, 17, 18, 24, 28], while in other cases, the subjects were limited to patients with severe COPD (and therefore greater susceptibility to bronchiectasis) [16, 21, 22, 27]. Furthermore, not all the studies investigated consecutive patients [24–26, 29, 31], or patients who had all undergone tomographic studies for the diagnosis of bronchiectasis or radiological phenotypes [3, 17–19, 25, 26, 28]—both of which are essential for our understanding of the real prevalence of bronchiectasis. The radiological criteria used to

diagnose bronchiectasis were not the same in all the studies, either. Sometimes a study's main objective was not the prevalence of bronchiectasis or its consequences, so tomography was used to analyze other findings, such as the quantification of emphysema [19]. Some studies were retrospective, just analyzing patients who had been subjected, for whatever reason, to a tomographic study at some point in the past [24–26, 29–31], while others established a previous diagnosis of bronchiectasis as a criterion for exclusion [18, 19, 22, 23, 27, 30]. A review of the literature to date furnishes us with 17 studies that provide information about the prevalence of bronchiectasis in COPD patients (Table 9.1) but only eight [16, 20–23, 27, 30, 31] of these studies present a methodology that allows these data to be treated with sufficient confidence (consecutive patients with COPD in a stable phase, all of them subject to an HRCT scan intended to analyze the presence or impact of bronchiectasis). In these eight studies, the range for the prevalence of bronchiectasis was narrower—at 14–52%. Interestingly, in all the studies that were analyzed, the prevalence was higher, regardless of the percentage that was calculated, when there was a greater severity of COPD (according to either functional criteria or the GOLD classification) [19–21, 27, 31]. Furthermore, most of the cases of bronchiectasis that were observed were not attributed to any other known etiologies (including α1-ATD), and they tended to present a similar radiological pattern: presence in the lower lobes, a cylindrical shape, and thickening of the bronchial wall due to the association with the bronchial inflammation that is typical of COPD.

However, as most cases of bronchiectasis appeared in severe COPD, and therefore mainly in elderly patients, there could be an overestimation of its real prevalence, since various studies have shown bronchial dilatations in healthy elderly patients that would satisfy the radiological criteria for bronchiectasis. A recent study by Tan et al., for example, used the Canadian series of 1,361 patients and observed that 19.1% of the subjects, with an average age of 68 who had never smoked, presented bronchial dilatations that would satisfy the radiological criteria habitually used for the diagnosis of bronchiectasis [31]. This suggests that Naidich's classic criterion (bronchoarterial quotient >1) [32] is not optimal for the diagnosis of bronchiectasis in patients with COPD, and it is therefore possible that there is a need to add other significant criteria, such as thickening of the bronchial wall or a secondary clinical picture compatible with bronchiectasis (both factors that are not usually found in bronchial dilatations solely due to age). Finally, it is important to take into account (in any analysis of the real prevalence of bronchiectasis in COPD patients) the possibility of false positives and negatives when interpreting HRCT, due to changes in the bronchoarterial quotient in patients with alterations in the caliber of pulmonary vascularization or transitory functional dilatations sometimes found in COPD patients, as well as the existence of diseases or images (cysts, boils, pneumatoceles, etc.) that can simulate bronchiectasis [33].

Large international registers of COPD patients, or the systematic application of tomographic studies in large-scale studies on thousands of COPD patients, could help us calculate the real prevalence of bronchiectasis in these patients [34].

Table 9.1 Characteristics of the studies analyzing the prevalence and outcomes related to bronchiectasis in COPD patients

Study (year)	*n*	Age (years)/gender	Study design	Stable COPD	Bch as main objective	Bch criteria	BCH prevalence	Main outcomes related to Bch
O'Brien et al. [3]	110	66.5 58% males	Prospective	No	No	Naidich and Hansell	**29%**	Increased sputum purulence Decrease FEV1 in cystic bch
Patel et al. [16]	54	69	Prospective	Yes	Yes	Naidich and Smith	**50%**	Increased airway inflammation and bacterial load Prolonged exacerbations
Roche et al. [17]	118	68.4 (12.1) 74% males	Prospective	No	No	Bronchi/vessel (diameter) >1	**19.8%**	Positive sputum culture
Garcia-Vidal et al. [18]	88	72.1 (10) 95% males	Prospective	No	No	Lobe number	**52%**	No relationship with FEV1, BODE index, PA isolation or 6 MWT
Agusti et al. [19]	2164	63.4 (7.1) 65% males	Prospective	Yes	No	No criteria available	**4%** Stage II: **1–2%** Stage III: **3–6%** Stage IV: **7–9%**	–
Bafadhel et al. [26]	75	67 (43–88) 58% males	Cross-sectional	Yes	CT scan COPD phenotypes	Naidich	**27%**	No relationship with lung function, exacerbations or bacterial load

Study (year)	*n*	Age (years)/gender	Study design	Stable COPD	Bch as main objective	Bch criteria	BCH prevalence	Main outcomes related to Bch
Martinez-Garcia et al. [27]	92	71.3 (9.3) 99% males	Prospective	Yes	Yes	Naidich	**57.6%** 34.7% moderate 72.5% severe	Risk factors for Bch were severe COPD, PPM isolates and at least one hospitalization in the previous year
Arram and Elrakhawy [20]	69	59.4–60.4 95% males	Cross-sectional	Yes	Yes	No criteria available	**47.8%** Moderate **31.3%** Severe **62.2%**	Severe exacerbations Time to recovery Decrease FEV1 Bacterial colonization
Stewart et al. [21]	3752	62.8–65.5 55% males	Prospective	Yes	Yes	Visual assessment	**20.8%** GOLD II: 18.8% GOLD III: 24% GOLD IV: 24%	Increased age, exacerbations, BODE and GOLD stage Decreased FEV1 and BMI
Martinez-Garcia et al. [22]	201	70.3 (8.9) 90.5% males	Prospective	Yes	Yes	Naidich and Bhalla	**57.2%**	Increased mortality, exacerbations, bacterial isolation including PA and CRP levels

(continued)

Table 9.1 (continued)

Study (year)	*n*	Age (years)/gender	Study design	Stable COPD	Bch as main objective	Bch criteria	BCH prevalence	Main outcomes related to Bch
Tulek et al. [23]	80	68 (8) 95% males	Cross-sectional	Yes	Radiological COPD phenotypes	Naidich and Bhalla	**33.8%** -40% in moderate-to-severe patients	Increased exacerbations, Bhalla score, CRP and ESR concentrations Decreased FEV1
Gallego et al. [28]	118	69.5 (8.2) Predominantly males	Prospective	No	No	Naidich and Smith	**47%**	Risk factor for PA isolation Mortality was higher in the PA group C.C. by mucoid PA was associated with Bch (score > 5)
Gatheral et al. [24]	406	71 (11) 56% males	Retrospective	No	Yes	Naidich	**69%**	Bch severity correlates with BWT but not with emphysema Bch related to PA and NTM isolation, and annual respiratory admissions, lower Charlson index and in-patient days but not to survival

Study (year)	*n*	Age (years)/gender	Study design	Stable COPD	Bch as main objective	Bch criteria	BCH prevalence	Main outcomes related to Bch
Jairam et al. [25]	338	71 (61–76) 54% males	Prospective	Yes	No	Fleischner criteria	**32.5%**	No relationship with future exacerbations or death
Mao et al. [29]	896	66.2 (9.6) 85% males	Retrospective	Yes	Yes	Naidich	**34.7%**	PA colonization Increased all-cause mortality
Doria da Silva et al. [30]	65	64.2 (8.5) 66% males	Retrospective	Yes	COPD phenotypes on HRCT	Bhalla	**33.8%**	No relationship with functional variables
Tan et al. [31]	451	62.8–69 years 46–50% males	Prospective	Yes	CT abnormalities including bch	Fleischner criteria	Mild 14.1% Moderate 22.2% Severe 35.1%	Increased chronic phlegm, wheezing, dyspnea and CAT score >10. No relationship with exacerbation frequency

Bch bronchiectasis, *COPD* chronic obstructive pulmonary disease, *HRCT* high-resolution computed tomography, *ESR* erythrocyte sedimentation rate, *PA Pseudomonas aeruginosa*, *CC* chronic colonization, *CRP* C-reactive protein, *BMI* body mass index, *PPM* potentially pathogenic microorganism, *6MWT* 6-minute walking test

9.4 The Prevalence of COPD in Bronchiectasis Patients

Although no study has yet demonstrated a causal relationship between COPD and bronchiectasis, most of the etiological tables for bronchiectasis increasingly include COPD as a cause, or, at the very least, a disease associated with bronchiectasis. COPD only began to appear in these tables a few years ago, reflecting the researchers' growing interest in the relationship between the two diseases. Thus, whereas Pasteur et al. (2000) [35], King et al. (2006) [36], and Shoemark et al. (2007) [37], do not mention COPD in the tables of etiologies and diseases associated with bronchiectasis in their respective studies, in 2013 Anwar et al. [38] published a study on 189 patients in which they found that 23% presented COPD as an associated disease. Subsequent larger studies, such as that of Lonni et al. [9] on 1,258 patients from various European series, observed that 15% (range 2.4–16%) presented COPD, which makes bronchiectasis the most frequent cause (or association), after post-infectious etiology. Moreover, the higher the prevalence of bronchiectasis, the greater its severity (2.8% had mild bronchiectasis and 22% severe), and the profile of patients with the two diseases in association corresponded with that of COPD patients (elderly male smokers). Gao et al. [39] recently published a systematic review of 8,608 patients from 56 studies (including that of Lonni et al.) and found that 3.3% of the bronchiectasis patients presented with COPD, although in some of these studies the presence of COPD or asthma was a criterion for exclusion. The percentage of COPD was higher in Europe than in Asia or North America. Finally, a recent etiological study (not covered by the systematic review of Gao et al.) of the Spanish historic register of bronchiectasis [10], comprising 2,047 patients, showed that 7.8% of patients with bronchiectasis presented associated COPD. The coexistence of the two diseases was reflected by more marked clinical, functional, and prognostic repercussions. Similarly, Goeminne et al. [40] observed how this subgroup of bronchiectasis patients with associated COPD had a higher mortality rate than other etiologies, with COPD a factor that was independently associated with this higher rate (along with age and radiological extension). It is not yet known whether the previous presence of bronchiectasis can accelerate the development of subsequent COPD in a patient who smokes, or whether it could explain the high proportion of bronchiectasis patients with COPD found in some series. In any case, it is often extremely difficult to establish a primary diagnosis in these patients, which makes it especially important to examine a patient's anamnesis and clinical history as fully as possible in order to verify the diagnosis [13].

9.5 Impact of Bronchiectasis on COPD Patients

Regardless of the real prevalence of bronchiectasis in COPD patients, most studies have concluded that its presence has a negative impact on COPD in clinical, functional, microbiological, inflammatory, and prognostic terms. Two recent meta-analyses demonstrate this impact very clearly. Du et al. [8] covered 14 studies with 5,329 COPD patients, of whom 1,572 (29%) presented with bronchiectasis, while

Ni et al. [7] examined six studies with 881 patients and found a prevalence of bronchiectasis of 54.3%.

Table 9.2 shows the main results of these meta-analyses, expressed as either the weighted mean difference (WMD) or OR (CI 95%) of patients with bronchiectasis associated with COPD, compared to those patients without bronchiectasis.

The above table allows us to conclude that although the studies are very heterogeneous in terms of methodology (as the authors themselves recognize), COPD patients with associated bronchiectasis present specific characteristics, whether clinical (older age, higher proportion of males, heavier smoking, greater production of sputum, and greater number of exacerbations), functional (greater airway obstruction), inflammatory (greater systemic inflammation), microbiological (more PPM isolates, including *Pseudomonas aeruginosa*), or prognostic (higher mortality rate). Of all these factors, two are particularly striking: on the one hand, patients with COPD and bronchiectasis are twice as likely to present exacerbations than the others, and on the other, they are four to seven times more likely to present chronic colonization by PPM. This could suggest—although it is still a hypothesis—that the presence of a chronic bronchial infection and inflammation, and a temporary increase in this inflammation due to more exacerbations, could trigger bronchiectasis in these patients, or worsen any pre-existing bronchiectasis.

Finally, another key aspect is the fact that bronchiectasis doubles the probability of death in COPD patients, after adjusting for confounding variables (including age and the severity of the COPD itself). Four studies [22, 24, 27, 41] have analyzed this

Table 9.2 Main results of the meta-analyses published on the relationship between COPD and bronchiectasis

	Du et al. [8] 14 studies ($n = 5329$)	Ni et al. [7] six studies ($n = 881$)
Bronchiectasis prevalence	29%	54.3%
Males	–	1.62 (1.15–2.28); $p = 0.006$
Age	–	WMD: 1.8 years (0.05–3.55; $p = 0.04$)
Smoking history	–	WMD 4.63 pack-years; 1.61–7.65; $p = 0.003$)
More daily sputum production	–	2.30 (1.66–3.19; $p < 0.00001$)
More exacerbations (previous year)	OR 1.97 (1.29–3)	WMD 1.54 (0.56–2.53; $p = 0.002$)
Lower FEV_1/FVC ratio	–	WMD −8.05% (−10.65 to −5.45)
Lower post-bd FEV_1 predicted severe airflow obstruction	1.31 (1.09–1.58)	WMD −11.06 (−18.27 to −3.85)
CRP level	–	WMD 6.11 (0.26–11.95)
Albumin level	–	WMD −0.14 (−0.23–0.06)
Chronic PPM colonization	OR 3.76 (2.37–5.96)	OR 7.33 (4.61–11.67)
Isolation *P. aeruginosa*	OR 4.75 (1.25–18.04)	OR 3.59 (1.89–6.47)
Mortality	1.96 (1.04–3.70)	

WMD weighted mean difference, *PPM* potentially pathogenic microorganism, *CRP* C-reactive protein; *P aeruginosa*, *Pseudomonas aeruginosa*, *OR* odds ratio

relationship to date, and three of them found this excess of mortality, with an OR of between 3.96 and 2.15. (One of these studies was published as an abstract.) Only Gatheral et al. [24] failed to demonstrate this association.

9.6 The Relationship of COPD-Bronchiectasis with Other Clinical Phenotypes of COPD

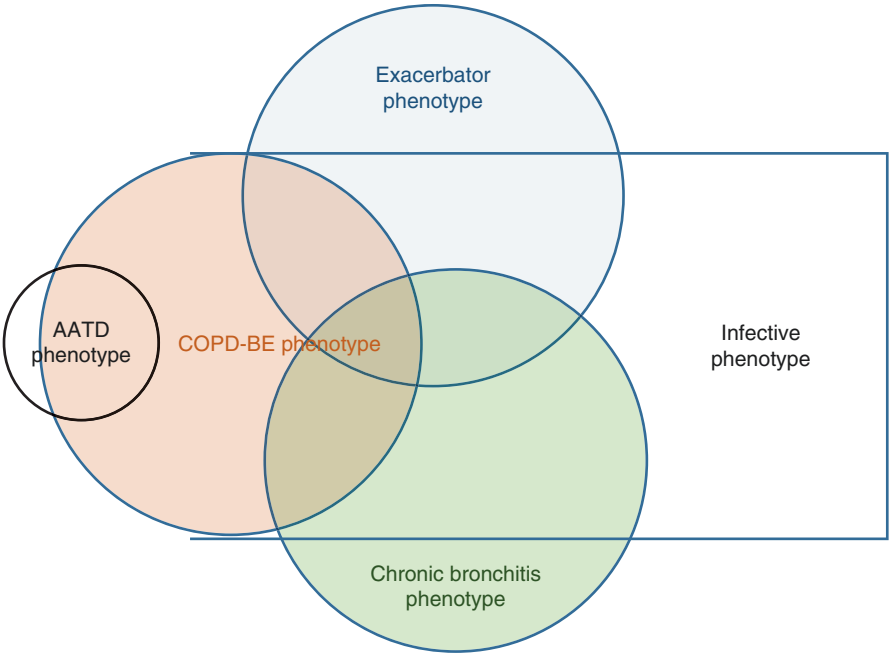
Research into these different clinical and prognostic characteristics has led some authors to consider this subgroup of patients with both COPD and bronchiectasis to be a special clinical phenotype [13–15], according to the classic definition of a clinical phenotype of COPD used by Han et al. in 2010 [42]. This proposal is endorsed by the therapeutic implications of this association, as the various international guidelines for both COPD and bronchiectasis indicate that in patients with both—sometimes called BCOS (Bronchiectasis-COPD Overlap Syndrome)—along the lines of ACOS (Asthma-COPD Overlap Syndrome) for asthma, each disease must be treated separately.

Studies of the relationship between COPD and bronchiectasis have shown that these patients experience more exacerbations and greater chronic expectoration. This means that the COPD-bronchiectasis phenotype may be closely linked to other already well-known phenotypes of COPD, such as the exacerbator [43] and chronic bronchitis phenotypes [44]. Moreover, there is still controversy as to whether, as some studies affirm, the radiological presence of emphysema (emphysematous phenotype) can be a marker of bronchiectasis (over and above the confirmed relationship of bronchiectasis with patients with α1-ATD (11, 12)). The COPD-bronchiectasis phenotype may therefore be an entity in its own right, but it has close links with some of the other previously established COPD phenotypes (Fig. 9.1).

Other authors have claimed that the COPD-bronchiectasis clinical phenotype could be considered a sub-phenotype or subgroup of patients within a broader phenotype that could be called the "infectious COPD phenotype" [45]. This phenotype would comprise those COPD patients (with or without bronchiectasis) who present a chronic bronchial infection by PPM. This would lead to a greater number of exacerbations as well as chronic expectoration resulting from more bronchial inflammation, although this sequence of events is still a hypothesis that has to be verified.

9.7 COPD and Bronchiectasis. Is There a Causal Relationship?

Although it is not yet known whether there is a causal relationship—with COPD the cause and bronchiectasis the consequence—there are a number of pathophysiological hypotheses that could explain this possible relationship, as shown in Fig. 9.2. COPD patients (especially moderate and severe cases, with a greater prevalence of bronchiectasis) often present a bronchial infection by PPM, with a consequent increase in bronchial inflammation and subsequent greater probability



AATD*: Alpha 1 antitrypsin deficiency; BE*: bronchiectasis.

Fig. 9.1 Relationship of the COPD-Bronchiectasis clinical phenotype with other possible COPD phenotypes. *AATD** alpha 1 antitrypsin deficiency, *BE** bronchiectasis

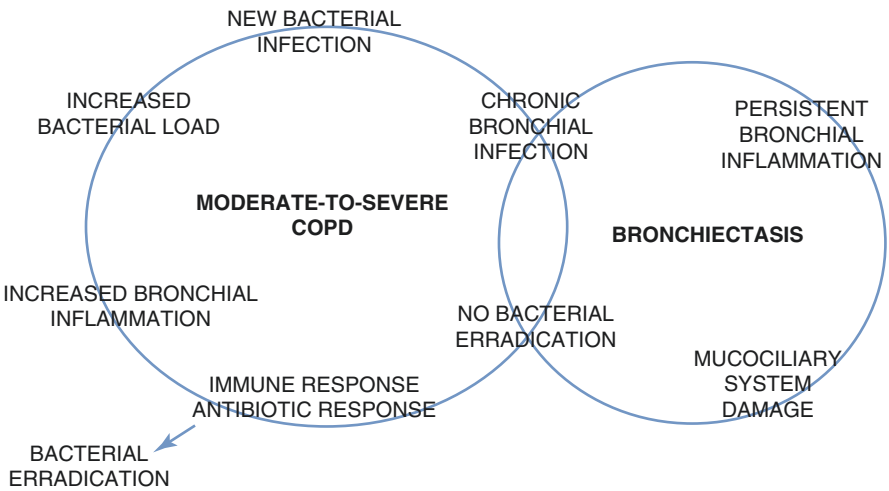


Fig. 9.2 Pathophysiological hypothesis for the development of new bronchiectasis in patients with COPD

of exacerbations [46, 47]. In such cases, the implementation of antibiotic treatment, along with the activation of the patient's immunological mechanisms, usually succeed in eradicating the bacteria. On other occasions, however, the infection is not eradicated—due to an inappropriate antibiotic treatment or a deficient immune system, or to other unknown (possibly genetic) causes—and it therefore turns into a chronic bronchial infection, leading to chronic inflammation [48]. It has long been known that both chronic bronchial infection and inflammation can damage the mucociliary escalator of the bronchial mucosa, which would encourage the growth of bacteria and boost inflammation, despite the antibiotic treatment. Both proteolytic and neutrophilic bacterial products, and an increased concentration of other pro-inflammatory molecules, would trigger the destruction of the bronchial wall, with the subsequent dilation of the thickened bronchial wall that we know as bronchiectasis. Although this entire process is hypothetical, it is biologically plausible and would represent a major advance in our understanding of the development of bronchiectasis in COPD patients [49].

From a clinical point of view, the confirmation of COPD as a cause of bronchiectasis requires longitudinal studies with HRCT on series of COPD patients without bronchiectasis. These studies should have an extended follow-up, to allow time for the development of bronchiectasis. Furthermore, it must be ensured that the HRCT cut-offs use the same technique and positions and, finally, that no pathology that could cause bronchiectasis independently of COPD appears between one HRCT and another. The follow-up should identify which variables are temporarily associated with the emergence of any new bronchiectasis or the growth of pre-existing ones, with a special emphasis on an exhaustive collection of data on bronchial inflammation (chronic or otherwise) and clinical and microbiological parameters, particularly exacerbations and the appearance of sputum.

9.8 Therapeutic Aspects

Regardless of whether the co-existence of COPD and bronchiectasis is a matter of chance or a real association between the two, most international guidelines on the treatment of both COPD and bronchiectasis recommend that the two diseases be treated separately [1, 5, 6]. This is particularly important as the scientific evidence has revealed enormous differences in the effects of some treatments on COPD and bronchiectasis. For example, short- and long-acting beta adrenergics and anticholinergics, phosphodiesterase-4 inhibitors, xanthenes, and inhaled steroids have proved more effective in COPD patients [1], while other drugs, such as macrolides, inhaled antibiotics, hypertonic substances, and respiratory physiotherapy, have shown greater efficacy in bronchiectasis patients [5, 6]. In any case, many of the treatments for COPD patients are used by extrapolation in bronchiectasis patients, in both the clinical stability and exacerbation phases, despite the paucity of the supporting evidence. (This is particularly true of bronchodilators, and both systemic and inhaled steroids.) Some of these clinical factors demand special attention. On the one hand, particular care must be taken with the use of inhaled steroids in bronchiectasis

patients, especially those with chronic bronchial infection by PPM, on account of their immunosuppressive properties. Although no study has demonstrated deleterious effects on these patients from the use of inhaled corticoids, there is some evidence to suggest that the use of inhaled steroids in COPD patients can produce an excess of infectious processes [50]. Until further studies throw more light on this situation, caution must be exercised in this respect.

On the other hand, macrolides at immunomodulatory doses could be especially useful in patients with associated COPD-bronchiectasis (particularly those with multiple exacerbations or abundant expectoration despite appropriate baseline treatment), as they have demonstrated their effectiveness in both COPD [51] and, above all, bronchiectasis [52–54]. There is also a need for studies that analyze the role of other anti-inflammatory drugs, such as phosphodiesterase-4 inhibitors, which are currently indicated for COPD patients with the chronic bronchitis phenotype [1], a significant percentage of whom could present bronchiectasis.

The use of inhaled antibiotics in patients with both COPD and bronchiectasis deserves a chapter of its own. This treatment should be applied in accordance with the recommendations of the international guidelines on bronchiectasis, especially in patients with chronic bronchial infection by *P. aeruginosa* and multiple exacerbations [4, 5]. However, there is a potentially interesting line of research on the effects of these drugs as a preventive measure against bronchiectasis in patients with COPD and chronic bronchial infection by PPM (especially *P. aeruginosa*) who have not yet developed bronchiectasis. One appropriate target could be COPD patients with chronic bronchial infection by PPM and multiple exacerbations triggered by these PPMs, despite suitable baseline treatment. The inhalation of antibiotics has the advantage of allowing high concentrations of a drug into the airways with few side effects. This enables them to be used at high doses over prolonged periods, with a subsequently greater probability of eliminating (or at least reducing) these patients' bacterial loads [55].

9.9 Bronchiectasis and Emphysema

It was previously thought that emphysema involved parenchymal destruction, while bronchial lesions represented a component of chronic bronchitis, but this concept has now been rejected. In recent years, bronchiectasis has been easy to diagnose in clinical practice with HRCT. Furthermore, more comprehensive screening of the COPD population has revealed that bronchiectasis is a prominent feature of this disease. The prevalence of bronchiectasis is high in patients with moderate-to-severe COPD, and it has been associated with exacerbations and bacterial colonization. Moreover, bronchiectasis is associated with an independent increased risk of all-cause mortality in COPD patients [22, 27]. Only a limited number of studies have assessed the specific association between bronchiectasis and emphysema, which is a component of COPD. Furthermore, there is some information available on the prevalence and impact of bronchiectasis in α1-ATD emphysema.

9.10 Bronchiectasis and α1-Antitrypsin Deficiency Emphysema

α1-ATD is a genetic condition that predisposes to an early onset of pulmonary emphysema and airway obstruction. It is well known that emphysema is the predominant component of COPD in α1-ATD deficiency, but the prevalence and impact of airway disease are greater than previously thought. Some reports have suggested an association between emphysema and bronchiectasis, and a causal link has also been postulated [11] (Fig. 9.3). A significant percentage of patients with α1-ATD have airway reactivity with wheezing, and approximately 40% of them have chronic coughs and sputum expectoration. Dowson et al. found that patients with chronic sputum production had worse airflow obstruction, more serious emphysema, poorer health status, and more exacerbations [56]. There is evidence to suggest that airway disease is an early and integral component of the pathogenesis of α1-ATD.

One possible hypothesis from the many airway-disease phenotypes described in α1-ATD is that unopposed human neutrophil elastase (HNE) is present in both the airways and the lung parenchyma. Bronchial connective tissue in the airway is injured when protease inhibitor deficiency is present, since normal microbial and native airway cellular interactions may be amplified [57]. It is still uncertain, however, whether bronchiectasis is a primary feature of the disease or a result of airway damage caused by recurrent infection; it is also not yet known whether viral or bacterial infections play a crucial role in airway disease in α1-ATD. The clinical airway diseases found in α1-ATD are heterogeneous, as they include asthma, chronic bronchitis and bronchiectasis. In the NHLBI Registry study in the United States, which included 1,129 patients, a history of asthma was reported in 35% of the cohort, while the clinical diagnosis was confirmed in 21%; reversible airflow obstruction was seen in 61% of the patients [58].

The frequency of bronchiectasis in α1-ATD is difficult to ascertain because the disease is relatively uncommon and its prevalence varies from one study to another

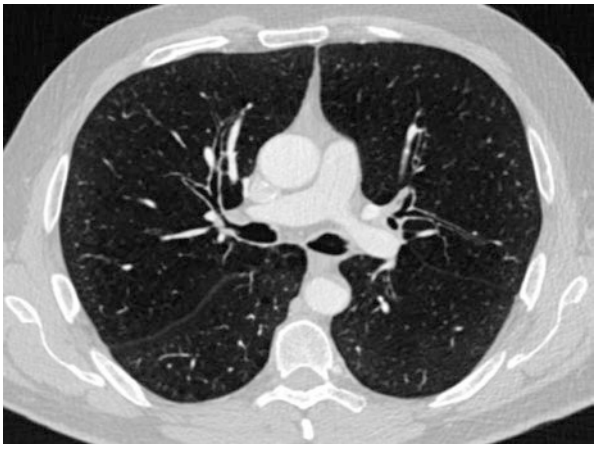


Fig. 9.3 HRCT image of a 70-year-old COPD patient with emphysema and bronchiectasis

(27–60%). There is some controversy over whether bronchiectasis is a frequent clinical phenotype in α1-ATD. Population-based bronchiectasis registries have not shown any great differences in AAT allele frequencies, compared with control populations. However, studies of α1-ATD cohorts have found more frequent bronchiectasis. In the 14 patients studied by King et al., the prevalence of bronchiectasis was 43%, and patients with bronchiectasis had a significantly higher infection score than those without. Interestingly, the presence of bronchiectasis was greater in lobes in which the emphysema score was higher, maybe because the association between emphysema and bronchiectasis reflects a regional interaction between the underlying pathogenic processes [12].

Parr et al. [11] investigated the prevalence and impact of bronchiectasis in 74 patients with α1-ATD (PI*ZZ). CT bronchiectasis was found in 70 patients (95%), while the clinically significant disease, manifested by four or more segments of airway abnormality and chronic sputum production, was detected in 20 patients (27%). There was a correlation between greater bronchiectasis severity and more severe emphysema, between airway disease scores and health status, and between bronchial wall thickening and FEV_1.The severity of the airway disease therefore had an independent effect on health status, after adjustment for the severity of emphysema. The most common morphological type was cylindrical bronchiectasis, although cases of varicose and cystic bronchiectasis were also described.

COPD exacerbations are common in α1-ATD, but only a few studies have investigated their frequency. A large, one-year cohort in the United Kingdom, for example, showed a prevalence of 54% [57]. Exacerbations are associated with the influx of PMN into the lung; when these PMN are activated, they release products, including HNE, in proportion to the airway bacterial load [59]. There is some controversy as to whether augmentation therapy with α1 AT alters the frequency of exacerbations [57, 60].

Microbiological organisms are associated with COPD exacerbations in α1-ATD in approximately 50% of cases, with *H. influenza* and *P. aeruginosa* as the most frequently isolated species. Microbiomes may also play a role in the genesis of COPD, or some of its phenotypes (particularly bronchiectasis) [57].

9.11 Bronchiectasis and Emphysema Other than α1-ATD

There have also been a few studies that reported an association between bronchiectasis and emphysema (as a component of COPD), other than α1-AT D, while the coexistence of emphysema and bronchiectasis in COPD patients is not unusual. Fugimoto et al. classified 172 patients with COPD into various phenotypes, according to their HRCT findings. They found that 25.6% of the patients had a combination of emphysema and bronchial wall thickening. Compared with the emphysema phenotype, these patients coughed and wheezed more, and produced more sputum; there were also higher rates of exacerbation and hospitalization, and greater reversibility of airflow limitation [61].

Gatheral et al. sought to determine the impact of bronchiectasis on clinical outcomes in 406 COPD patients, regardless of any coexisting emphysema. They found

that bronchiectasis is very common in COPD patients (69%) and that it is associated with increased hospitalization and respiratory infection due to *P. aeruginosa* and atypical mycobacteria, independent of the severity of any coexisting emphysema and bronchial wall thickening [24]. Bronchiectasis could have an impact on the course of COPD, over and above the effects of emphysema and bronchial wall thickening, by impairing mucociliary clearance, causing mucus stasis, and increasing bacterial colonization. This has potentially important implications for therapy [24].

However, the presence of emphysema in patients with bronchiectasis has been reported only rarely. In one retrospective study, Loubeyre et al. assessed the presence and extent of emphysema in 90 non-smoking patients with bronchiectasis diagnosed via HRCT. They found a high prevalence of emphysema in patients with bronchiectasis (45%), with the emphysema mainly located in the same bronchopulmonary segments as the bronchiectasis [62]. The presence of emphysema correlated with the extent and severity of bronchiectasis. Furthermore, those patients with CT evidence of emphysema had significantly greater airflow obstruction and trapped air than those without emphysema. The authors suggest that there may be a causal association between obstructive airway disease and emphysema, and that emphysematous developments are a consequence of bronchiolar inflammation.

There is evidence that emphysema may constitute a mortality risk factor in patients with bronchiectasis. Loebinger et al. retrospectively reviewed the CT images of 91 patients with bronchiectasis, and found that increased bronchial wall thickness and emphysema were the strongest predictors for mortality in bronchiectasis patients [63]. In a recent study, Goeminne et al. analyzed the risk factors for mortality in 245 patients with bronchiectasis [40] and found that the overall mortality was 20.4% in a follow-up period of 5.18 years, while patients with bronchiectasis and associated COPD showed a mortality rate of 55% in that period. The authors concluded that COPD was indeed a mortality risk factor in these cases.

Another retrospective study investigated the independent risk factors for mortality over 5 years in 89 patients recently diagnosed with bronchiectasis, 8 (9%) of whom also had emphysema. By the end of the study, 13.5% of the patients had died. Mortality was significantly associated with emphysema and the radiographic extent of bronchiectasis. Moreover, the latter variable was more severe—along with airflow limitation—in patients with associated emphysema than in those without it. Thus, the authors conclude that emphysema might be a risk factor for mortality in bronchiectasis and suggest, as a possible pathogenic explanation, that the presence of emphysema might be a result of inflammation in distal airways in response to the development of bronchiectasis, leading to a deterioration in lung function and a poorer prognosis [64].

9.12 Future Challenges

The questions to which we have found answers are far outnumbered by those that remain unanswered. Table 9.3 highlights some of the questions that need to be resolved if further advances are to be made with this association.

Table 9.3 Future challenges in the relationship between bronchiectasis and COPD

What is the real prevalence of bronchiectasis in COPD patients?
What is the prognostic impact of the presence of bronchiectasis in COPD patients?
Are the usual radiological criteria for bronchiectasis valid in COPD patients?
What is the role of exacerbations and chronic bronchial infection by PPM?
Is COPD-bronchiectasis a different phenotype than COPD?
Is COPD capable of triggering bronchiectasis?
Is bronchiectasis a mere comorbidity, or just a phase in the natural history of a COPD?
In which COPD patients should the presence of bronchiectasis be ruled out?
Which pathophysiological mechanisms associate COPD with bronchiectasis?
Why don't all COPD patients present bronchiectasis?
Why don't all COPD patients present chronic bronchial infection by PPM?
What are the predictive biomarkers of bronchiectasis?
What is the role of anti-inflammatory drugs (macrolides or phosphodiesterase-4 inhibitors) in these patients?
Do inhaled steroids have a deleterious effect on these patients?
What are the role and indications of inhaled antibiotics?
What role does the modification of the microbiome play in these patients?
What is the pathophysiological association between bronchiectasis and α1-ATD?
Do inhaled and intravenous augmentation therapy help both emphysema and airway disease in α1-ATD?
What are the prevalence and the impact of emphysema in bronchiectasis?
Should a future therapeutic approach target both components?

Conclusions

The relationship between COPD and bronchiectasis harbors many questions that still have to be answered. It is reasonable to suppose that the presence of a persistent chronic bronchial infection by PPM in COPD patients could be the gateway for the development of bronchiectasis, but this causal relationship has not yet been proven. Nevertheless, it does seem that the presence of bronchiectasis (especially when associated with bronchial wall thickening and a clinical picture differentiating it from the bronchial dilatations that are typical of old age) has a negative impact on symptoms and treatment, and possibly the prognosis of COPD patients. This means that the COPD-bronchiectasis overlap syndrome could represent a true clinical phenotype of COPD, closely linked with other phenotypes (e.g., exacerbator and chronic bronchitis). On the other hand, bronchiectasis is more common and severe where emphysematous lesions are also present, and it may increase the severity of the disease and worsen health status, especially in patients with α1-ATD. Further studies are needed to resolve all these unanswered questions, but everything suggests that the combination of chronic bronchial infection, bronchiectasis, and COPD (with or without emphysema) represents a serious entity.

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Other Predisposing Factors for Bronchiectasis

10

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Bronchiectasis is an umbrella term for patients with a chronic inflammatory lung disease characterised radiologically, by the permanent dilation of bronchi, and clinically, by persistent cough, sputum production, recurrent respiratory tract infections and general malaise [1]. Data across multiple healthcare systems suggest that the prevalence of bronchiectasis is increasing [2–4] Whether this represents a real increase in disease burden, perhaps in relation to improved longevity of the population and the chronic nature of the diseases that cause bronchiectasis, or is an ascertainment bias due to increased pick-up rates in an era when improved sensitivity high-resolution computed tomography (HRCT) scans are routinely being performed is difficult to determine.

Bronchiectasis is the third most common chronic obstructive lung disease but is often dwarfed by its highly prevalent cousins, asthma and chronic obstructive lung disease (COPD). Unlike these conditions, bronchiectasis requires an imaging test for diagnosis, i.e. HRCT, and inevitably cases are missed due to misdiagnosis or failure to recognise that patients may have dual airway disease. Ambiguity in radiological interpretation may also contribute with two case series reporting that approximately 15% of radiologically diagnosed patients had their bronchiectasis diagnosis refuted on re-read of their scans by an expert thoracic radiologist [5, 6]. Another fascinating phenomenon is how long patients have been symptomatic prior to diagnosis which can be up to nearly two decades [7]. This suggests that the index of suspicion for bronchiectasis remains low in the respiratory and non-respiratory health community. It also suggests that the disease accelerates over time in keeping with Cole's "vicious cycle" hypothesis whereby infections become more frequent and severe as the airway inflammation intensifies [8, 9].

Determining the aetiology of bronchiectasis can be highly challenging. According to a recent systematic review on aetiology of bronchiectasis in adults, in approximately 45% of patients, it is seemingly a primary airway disease and, in others, a complication of a number of other highly heterogeneous disorders (Table 10.1)

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Table 10.1 Breakdown of aetiologies of bronchiectasis according to recent systematic review [10]

Risk factors	Total number	% of total
Idiopathic bronchiectasis	3857	44.8
Postinfective bronchiectasis	2574	29.9
Immunodeficiency	429	5.0
Chronic obstructive pulmonary disease	333	3.9
Connective tissue disease	328	3.8
Allergic bronchopulmonary aspergillosis	223	2.6
Ciliary dysfunction	218	2.5
Asthma	120	1.4
Inflammatory bowel disease	66	0.8
Obstructive	67	0.8
Aspiration/gastro-oesophageal reflux	64	0.7
Congenital malformation	33	0.4
α_1-Antitrypsin deficiency	36	0.4
Diffuse panbronchiolitis	27	0.3
Young's syndrome	26	0.3
Pink's disease	20	0.2
Yellow nail syndrome	11	0.1
Bronchiolitis obliterans	3	<0.1
Others[a]	221	2.6

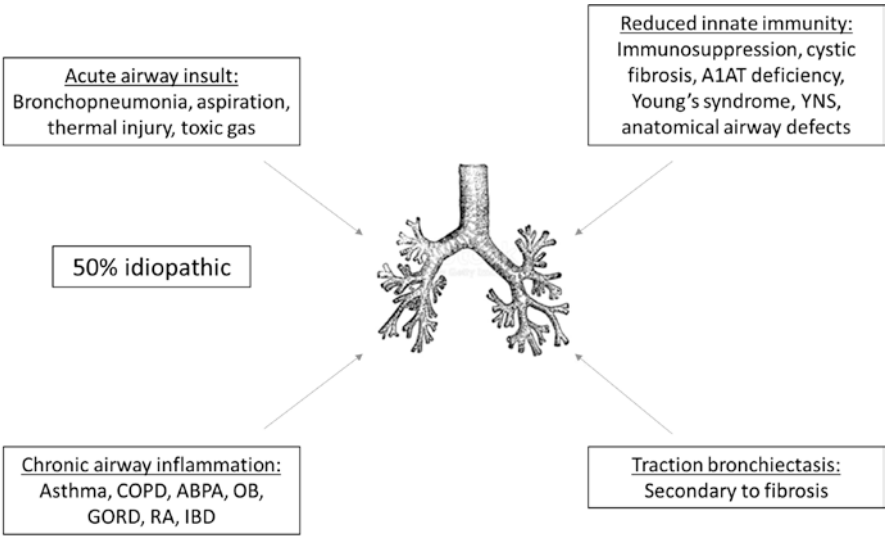
[a]Other aetiologies include sinobronchial syndrome (n = 27), amyloid (n = 1), smoke inhalation (n = 1), eosinophilic bronchiolitis (n = 1), bronchiolitis obliterans (n = 3), vasculitis (n = 5), interstitial lung disease (n = 63), cystic fibrosis or cystic fibrosis transmembrane conductance regulator-related bronchiectasis (n = 20), systematic disease (n = 47) and other unreported (n = 42)

[10]. History taking is extremely important in determining the most likely aetiology. Finding conditions that have a known association with bronchiectasis does not necessarily mean that they are causal. It can be very difficult if a patient has an existing airway disease: is the diagnosis primary bronchiectasis, asthma or COPD complicated by bronchiectasis? Similarly, in systemic disorders, such as rheumatoid arthritis (RA), is the bronchiectasis part of the disease process that may even precede the joint disease or is it due to pulmonary infection in an immunosuppressed host? Accurate determination of aetiology can have important therapeutic and prognostic implications. Tailoring treatment is particularly likely to benefit patients with immunodeficiency states, allergic bronchopulmonary aspergillosis (ABPA), recurrent aspiration and patients with very focal bronchiectasis who may benefit from lung resection. In this chapter we will discuss aetiologies of bronchiectasis not covered in previous chapters, outlining the associations between different diseases, the impact of these relationships and the therapeutic considerations. Our group finds it useful to think of aetiology in the following framework (Fig. 10.1).

10.1 Acute Airway Insult

10.1.1 Postinfectious Bronchiectasis

Postinfectious bronchiectasis is the commonest known cause of bronchiectasis accounting for approximately 20–30% of all cases, i.e. a bronchopneumonia that



Abbreviations: COPD: chronic obstructive pulmonarydisease; ABPA: allergic bronchopulmonary aspergillosis; OB: obliterative bronchiolitis; GORD: gastro-oesophageal reflux disease; RA: rheumatoid arthritis; IBD: inflammatory bowel disease, A1AT: alpha-1 anti-trypsin deficiency; YNS: yellow nail syndrome.

Fig. 10.1 Aetiological framework for bronchiectasis. *COPD* chronic obstructive pulmonary disease, *ABPA* allergic bronchopulmonary aspergillosis, *OB* obliterative bronchiolitis, *GORD* gastro-oesophageal reflux disease, *RA* rheumatoid arthritis, *IBD* inflammatory bowel disease, *A1AT* alpha-1 antitrypsin deficiency, *YNS* yellow nail syndrome

damages the bronchi, triggering the vicious cycle process [11–13]. Bacterial infections include childhood pertussis, bacterial pneumonia, *Mycobacterium tuberculosis* and nontuberculous mycobacteria (NTM). Viral infections include childhood measles, adenoviruses, influenza and human immunodeficiency virus (HIV). Fungal infections include *Histoplasma* and *Aspergillus* infections.

Retrospective reporting in adults of a significant childhood lower respiratory tract illness is very common in bronchiectasis patients and may be limited by recall or reporter bias. However, the severity of that illness is often unquantifiable, and the time lag from when the patient started suffering from repeated bronchitis following this herald infection is often unclear and difficult to interpret as causal [7, 11]. Indeed, there is no definition of within what maximum latency period from first infection to when recurrent bronchitis develops is the aetiology deemed as postinfectious.

A 1998 observational UK cohort study following 1392 individuals from birth demonstrated that individuals with pneumonia before the age of seven had reduced lung function, compared to those without a history of childhood pneumonia, suggesting that early pneumonia may play a role in subsequent lower airway damage [14]. The pathophysiological connection between childhood infections of measles

and pertussis with bronchiectasis is poorly understood but is likely attributable to the development of secondary bronchopneumonia as a complication of the initial infection causing bronchial damage. *Mycobacterium tuberculosis* (TB) may result in the development of bronchiectasis not only by direct tissue injury but also as a sequela of enlarged and caseous lymph nodes around bronchi or damaged airways that predispose to bacterial colonisation. TB remains endemic in parts of Asia and sub-Saharan Africa and is particularly prevalent among those living with HIV, with the combination augmenting morbidity and mortality of both disease processes. Immunosuppression caused by severe infections or other comorbidities or immunosuppressive therapies (including steroids and antitumour necrosis factor (anti-TNF) drugs), are also risk factors for the development of both TB and bronchiectasis.

Although the inciting infection is usually severe, bronchiectasis can also occur with minimal or silent infections. This is often the case when the inciting infection is caused by NTM, with *Mycobacterium avium* complex (MAC) most frequently identified. Similar to TB, NTM have traditionally been considered a secondary pathogen in immunocompromised hosts or in areas of damaged lungs. However, primary NTM infection associated with bronchiectasis in the right middle lobe and/or lingula in apparently normal hosts (primarily non-smoking, asthenic, females) has been well described (Lady Windermere syndrome) [15, 16].

ABPA is generally considered separately and represents a hyperimmune reaction to the *Aspergillus* organism rather than a true infection, characterised by an exaggerated T-helper cell response in patients with a long history of asthma that is resistant to bronchodilator therapy [17].

Accuracy in categorisation is important as some aetiological subgroups encountered in clinical practice are excluded from interventional studies [18]. Diagnostic delay is also more likely in patients with a postinfectious aetiology compared to idiopathic and other aetiologies [7]. A longer duration of symptoms of bronchiectasis is associated with worse lung function and poorer long-term outcomes [19]. No studies have interrogated the breakdown of postinfectious aetiologies in detail, so we do not know if age at time of initial insult or type of initial infection, e.g. viral versus bacteria and diffuse versus localised, affects bronchiectasis severity or long-term course of disease.

10.1.2 Direct Inhalational Injury

Inhaled substances may directly injure the pulmonary epithelium at various levels of the respiratory tract. This can range from foreign body obstruction, more common in children, to overt aspiration, often associated with either a reduced consciousness or difficulties in swallow coordination as a result of cerebrovascular attacks, seizures, intoxication or neurological disorders.

Bronchiectasis that results from foreign body inhalation generally occurs in the right lung and in the lower lobes or posterior segments of the upper lobes. Bronchiectasis is more likely to occur if there is significant delay between inhalation and extraction or if a post-obstructive pneumonia develops. One retrospective

study looking at children with persistent or recurring atelectasis of the right middle lobe and/or lingula despite conventional treatment found a positive correlation between the duration of symptoms and the development of bronchiectasis and demonstrated that an early and aggressive strategy of HRCT and interventional bronchoscopy was associated with reduced bronchiectasis *sequelae* [20].

Overt particulate aspiration, often consisting of unchewed food, or part of a tooth or crown, frequently triggers a post-obstructive pneumonia following mechanical obstruction to a bronchus by the retention or aspiration of infected secretions, resulting in incomplete resolution and predisposition to subsequent lung abscess [21]. Delayed or ineffective therapy and poor nutrition may contribute to prolonged pneumonitis with resultant focal bronchiectasis. Organic materials can cause severe inflammation in a short period of time with development of airway obstruction relatively earlier. In contrast, inorganic foreign bodies are inert; therefore patients might be initially asymptomatic for prolonged periods [21].

Bronchial obstruction predisposing to bronchiectasis can also be caused by intraluminal obstructing lesions such as carcinoid tumours or extraluminal compression from encroaching lymph nodes. It is important to identify the presence of airway obstruction because surgical resection may be required.

Thermal injury as a result of smoke inhalation may predispose to bronchiectasis directly, due to particulate matter of inorganic compounds that is small enough to easily infiltrate the lungs and initiate an inflammatory response, and indirectly, as a result of compromised immune function due to severe sepsis as a result of extensive burns [22]. Exposure to toxic gases, particularly high-dose ammonia, can result in residual bronchiectasis in survivors of the initial upper airway obstruction [23]. Disease severity and location are generally determined by the characteristics of inhaled substances such as water solubility, size of substances and chemical properties as well as individual susceptibilities.

10.2 Decreased Innate Immunity

10.2.1 Primary Ciliary Dyskinesia (PCD)

PCD is a rare, heterogeneous autosomal recessive genetic disorder with an estimated incidence of 1 per 10,000–20,000 births [24]. It is characterised by impaired mucociliary clearance due to abnormal ciliary ultrastructure or function, whereby cilia are either unable to beat (ciliary immotility), unable to beat normally (ciliary dyskinesia) or absent altogether (ciliary aplasia), producing a wide clinical spectrum of symptoms incorporating bronchiectasis, sinusitis, otitis media and subfertility [25]. *Situs inversus totalis* occurs in approximately 50% of patients with PCD due to defective embryonic nodal cilia and is termed Kartagener's syndrome when *situs inversus*, chronic sinusitis and bronchiectasis occur together.

Bronchiectasis in PCD patients is usually most marked in the lingula and right middle lobe (Fig. 10.2b). The reason for this is unclear, but the bronchi to these lobes are the most angulated to the main bronchial tree and may be more vulnerable

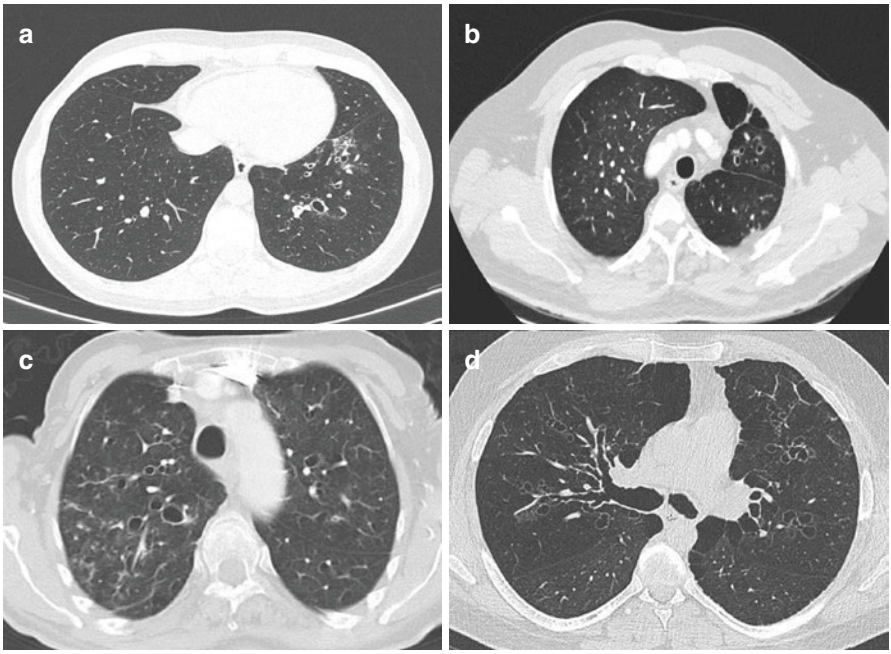


Fig. 10.2 Axial computed tomography (CT) images of the lower thorax in lung windows demonstrating cylindrical bronchiectasis and peribronchial wall thickening in (**a**) postinfectious bronchiectasis in a 39-year-old female who had left lower lobe pneumonia at age 7; (**b**) patient with primary ciliary dyskinesia with lingular predominant bronchiectasis; widespread bronchiectasis affecting all lung lobes in patients with (**c**) recurrent aspiration and (**d**) chronic obstructive pulmonary disease

in the presence of significant mucociliary dysfunction. A diagnosis of PCD may be somewhat challenging, requiring a well-described clinical phenotype combined with the identification of abnormalities in ciliary ultrastructure and/or function. Patients usually have marked upper airway disease, and 98% have had otitis media by middle teenage years [26]. An absence of sinusitis and otitis media, therefore, makes the diagnosis very unlikely.

If there is a high clinical suspicion, referral to a specialist centre is strongly recommended for rigorous diagnostic evaluation [27]. Nasal nitric oxide (nNO) analysis is a useful screening test for PCD. nNO levels in patients with PCD are generally low (10–20% of normal values, which range from 125 to 867 nl/min; mean, 287 nl/min); however, standardisation of nNO analysis and reporting is needed, with particular need for reference cut-off values for different analysers and respiratory manoeuvres [24]. nNO should not be used as an isolated diagnostic test because low levels are occasionally reported in patients with cystic fibrosis, sinusitis, nasal polyposis or other causes of nasal obstruction and acute infections.

Assessment of ciliary ultrastructure by transmission electron microscopy was previously considered the ‘gold standard’ test for PCD. Biological nasal or bronchial brush biopsies are obtained to allow assessment of ultrastructure and ciliary

beat frequency and pattern using high-resolution, high-speed video microscopy with slow-motion replay. However, as many as 30% of patients with a strong PCD clinical phenotype and low nNO reportedly have normal ciliary ultrastructure and/or subtle, non-diagnostic changes in ciliary waveform; therefore this technique cannot be used to rule out PCD [24, 25]. A combination of techniques including nNO, transmission electron microscopy and culture at air-liquid interface may all contribute to a diagnosis of PCD, but despite expert evaluation, results can remain inconclusive, and repeated testing is often required. Recent advances to identify the genes associated with PCD provide hope for genetic testing as an addition to diagnostic testing. It is currently estimated that genetic testing can detect 65% of patients with PCD, and genetic testing is increasingly used as an adjunct test, particularly for difficult-to-diagnose cases with undetermined ciliary ultrastructure or function studies and/or unusual clinical characteristics [28]. Recent guidelines for the diagnosis of PCD published by the European Respiratory Society address multiple facets of PCD diagnostic tests and whether or not they should be included in the diagnostic algorithm [29].

There are currently no therapies available that can reverse the underlying ciliary abnormalities in PCD and very limited data from randomised clinical trials to support any particular forms of therapy. Therefore the goals of therapy are consistent with the management of bronchiectasis in terms of routine airway clearance, the use of antibiotics to control infection and the elimination of exposure to inflammatory triggers.

10.2.2 Young's Syndrome

This syndrome describes male patients with a combination of bronchiectasis, sinusitis and obstructive azoospermia. Respiratory function in these patients is thought to be only mildly impaired with normal ciliary structure and function and normal spermatogenesis, with the azoospermia being due to obstruction of the epididymis by inspissated secretions. Previous studies have shown an absence of CF gene mutations in these patients. Given the decline in frequency of this diagnosis and the associated geographical differences attributed to the sale of calomel in British colonies worldwide, it has been suggested that exposure to mercury in childhood may have been a cause of Young's syndrome in men born before 1955 [30]. Another possibility is that some cases attributed to Young's syndrome are actually cases of PCD, and due to the availability of better diagnostic methods, in particular high-throughput genetic studies, these cases can now be correctly identified.

10.2.3 Anatomical Airway Defects

Tracheobronchomalacia refers to diffuse or segmental weakness of the trachea and/or mainstem bronchi. Tracheomalacia (Williams-Campbell syndrome—resulting from a deficiency of cartilage in fourth- to sixth-order bronchi), bronchomalacia and

tracheobronchomegaly can all lead to bronchiectasis via deficient clearance of respiratory secretions and the recurrent infections that result [31]. While airways appear dilated on imaging studies, the deficient cartilage support results in airways collapse during forced exhalation. Diagnosis requires an appropriate clinical history, the characteristic expiratory airway collapse and narrowing on radiological investigation, obstructive spirometry and exclusion of other causes of bronchiectasis. Pathology of the affected bronchi at bronchoscopy or CT bronchoscopy showing the deficiency of cartilaginous plates or absence of ring impressions in the bronchial wall is confirmatory [32].

Tracheobronchomegaly (Mounier-Kuhn syndrome) is characterised by distinct tracheobronchial dilation due to atrophy of the muscular and elastic tissues in the trachea and main bronchial wall. It occurs more commonly in males and is typically diagnosed in the third or fourth decades of life. Diagnosis is usually made on CT where abnormally large air passages are detected or at bronchoscopy, where dilation in the trachea and main bronchi during inspiration, and constriction and collapse during expiration and coughing may be evident. In adults, the diagnostic criteria are diameters of the trachea, >30 mm; of the right main bronchus, 20 mm; and of the left main bronchus, 18 mm [33]. Mounier-Kuhn syndrome involvement occurs at different levels: three subtypes have been described. In type 1, there is a slight symmetric dilation in the trachea and main bronchi; in type 2, the dilation and diverticula are distinct; and in type 3, diverticular and saccular structures extend to the distal bronchi. Ineffective cough consequent to pathologic dilation in the tracheobronchial tree and impaired mucociliary clearance leads to recurrent infections and bronchiectasis [34]. Connective tissue diseases, such as ankylosing spondylitis, Ehlers-Danlos syndrome, Marfan's syndrome and others have been associated with secondary tracheobronchial enlargement and should be considered in the work-up of these patients [34]. Treatment is generally supportive in terms of managing bronchiectasis with airway clearance and antibiotics to control infections.

10.2.4 Yellow Nail Syndrome

Yellow nail syndrome (YNS) is a rare disorder, in which there is a triad of nail discolouration and dystrophy, lymphoedema and chronic lung disease [35]. These can consist of chronic cough with sputum, recurrent respiratory infections, pleural effusions, bronchiectasis and rhinosinusitis. Onset tends to occur in the fourth to sixth decades with no gender predominance. It has previously been accepted that two of the triad are adequate for diagnosis [36]. The complete triad only occurs in one-third of patients where symptoms may occur years apart [37]. YNS has been associated with several autoimmune disorders, immunodeficiency states, immunosuppressive drugs and malignancy, particularly lymphoma [38–40]. The cause of bronchiectasis is unclear but may relate to impaired immune function or impaired secretion drainage, with subsequent increased infection risk. A recent case-control study of YNS and idiopathic bronchiectasis patients suggests that bronchiectasis in YNS is less severe than idiopathic bronchiectasis but is associated with increased mucus

plugging [41]. An increased association with *Aspergillus* sensitivity in the absence of peripheral eosinophilia nor clinical/radiological evidence of ABPA was also noted [41]. Long-term macrolide antibiotics may provide symptomatic relief and in some patients lead to resolution of dystrophic nails. Bronchiectasis patients with YNS should therefore be screened for impaired immunity, *Aspergillus* sensitivity and malignancy.

10.3 Chronic Airway Inflammation

10.3.1 Asthma

An interrelationship between asthma and bronchiectasis has long been suspected, but aetiological labelling in these patients may be misleading with many attributed as having idiopathic disease and asthma considered a comorbidity. Prevalence studies to date suggest a prevalence of 17.5–28% of bronchiectasis in asthma patients with no predilection for any particular lobes [27]. Patients with bronchiectasis may wheeze and have bronchial hyperresponsiveness without meeting criteria for asthma. However, there may be a specific phenotype of bronchiectasis with asthma that represents an independent risk factor for frequent exacerbations and increased mortality. In a database survey and large multicentre cohort, respectively, asthma (diagnosed based on clinical characteristics and reversible airflow limitation as per international guidelines) was found to be independently associated with bronchiectasis exacerbations and with a one to three times increase in mortality [42, 43]. Patients with asthma and bronchiectasis are more likely to present with increased neutrophilic bronchial and systemic inflammation, more wheezing, dyspnoea, cough and sputum production, have more frequent exacerbations and have more severely impaired health status compared with asthma alone. From the clinician's point of view, identifying asthma patients with bronchiectasis who have underlying neutrophilic inflammation that responds to prophylactic antibiotics may be of particular importance. More work is needed to better characterise these patients at a primary and secondary care level and ensure that their bronchiectasis is not ignored or misdiagnosed. Further clinical trials in this population are needed to evaluate their response to available treatments.

10.3.2 Alpha-1 Antitrypsin Deficiency (AATD)

The relationship between bronchiectasis and AATD remains a controversial issue. Some small initial series found bronchiectasis using chest HRCT in up to 40% of patients with AATD [44, 45]. Following a review of the clinical manifestations and chest CT scans of 74 patients with AATD, 70 (95%) were found to have radiographic abnormalities suggestive of bronchiectasis, 20 (27%) of whom presented clinically significant bronchiectasis. The most severe bronchiectasis was associated with the most severe emphysema, apart from one subgroup of patients with high

radiological bronchiectasis scores and little emphysema. Other studies, however, have failed to observe any relationship between bronchiectasis and AATD [12, 46]. In a case-control study, no excess frequency of AAT alleles was documented in patients with bronchiectasis, except for those who had both emphysema and bronchiectasis; the authors concluded that the bronchiectasis was probably a consequence of emphysema [46]. It is not known whether AATD has a common pathway that contributes to the simultaneous formation of emphysema and bronchiectasis or whether emphysema predisposes to bronchiectasis. Furthermore, the scarcity of data and longitudinal studies makes it impossible to determine whether these findings have any prognostic implications. Current guidelines recommend AAT testing in patients with bronchiectasis and no other evident aetiology given the potential for change in management with AAT augmentation therapy [27].

10.3.3 Gastro-Oesophageal Reflux Disease (GORD) and Chronic Pulmonary Microaspiration

Whether GORD is an aetiological factor in the development of bronchiectasis or simply a comorbidity is a current area of controversy, compounded by the lack of consensus of aetiological definitions in bronchiectasis. GORD is often grouped with overt aspiration in aetiological studies of bronchiectasis with inconsistency of diagnostic labelling and investigation significantly underestimating the true prevalence of objective GORD in patients with bronchiectasis. In other chronic lung diseases, GORD is generally considered to be a common comorbidity that contributes to worse pulmonary disease outcomes.

GORD is defined as symptoms or end-organ complications resulting from the reflux of gastric contents into the oesophagus, or beyond into the oral cavity, larynx or lung, when it is termed extra-oesophageal reflux (EOR) [47, 48]. In order for GORD to be pathogenic in bronchiectasis, there clearly has to be EOR present. The main factors that determine the significance of EOR include the frequency, duration and extent of reflux episodes as well as the volume, composition and destination of the refluxate. A diagnosis of GORD can be made using a combination of symptom presentation (including both typical and atypical symptoms), objective measurements and/or response to empiric antisecretory therapy [48, 49]. In the absence of typical symptoms, combined ambulatory 24-h oesophageal pH monitoring with multichannel intraluminal impedance is the current gold standard investigation of choice [49]. This technique allows the measurement of proximal versus distal reflux, acid versus weakly acid or non-acid reflux and measurement of gaseous versus liquid reflux, enabling confirmation of GORD in patients whose diagnoses may have been missed using pH testing alone.

GORD may also be associated with pulmonary microaspiration of gastric contents. Although pH-impedance monitoring detects reflux extending into the proximal oesophagus, the extent of reflux within the hypopharynx and airway, which may be more relevant in bronchiectasis, is not measured. The detection of pepsin and bile acids, markers of gastric and duodenal reflux, respectively, in saliva,

sputum, tracheal aspirates or bronchoalveolar lavage fluid has been shown in cystic fibrosis, bronchiectasis and other chronic lung conditions to exacerbate airway inflammation and colonisation and, in the future, may complement questionnaires as a screening tool to assist an office-based diagnosis of EOR in patients with bronchiectasis [50, 51].

The specific cause and effect relationship between GORD and bronchiectasis has not yet been fully elucidated and is likely to occur in a bidirectional manner. Studies to date demonstrate a prevalence of GORD in bronchiectasis ranging from 26% to 75% using a range of diagnostic techniques and have shown that GORD is associated with an increase in symptoms, exacerbations and hospitalisations, lobar disease extent, chronic infection with *Pseudomonas aeruginosa*, reduced pulmonary function, reduced health-related quality of life and an increased risk of mortality [5, 43, 50–56]. However, further clarification of these associations is needed with larger prospective longitudinal studies.

Possible mechanisms that may contribute to GORD in bronchiectasis originate from gastro-oesophageal dysfunction, including altered pressure in the lower oesophageal sphincter, the presence of a hiatal hernia and changes in oesophageal motility. Proposed respiratory contributions to the development of GORD include respiratory medications that may alter oesophageal sphincter tone and changes in respiratory mechanics, with increased cough and lung hyperinflation potentially compromising the diaphragm-oesophageal interface.

There are a range of medical and surgical options available for the treatment of GORD, and while extensive studies in this patient population have not been undertaken, this comorbidity may be amenable to treatment. Anti-reflux therapy in the form of azithromycin has been demonstrated to be highly effective in reducing exacerbation frequency in patients with non-CF bronchiectasis, which may in part be due to its prokinetic properties, although this requires further investigation. Successful outcomes have also been demonstrated in select bronchiectasis patients undergoing Stretta radiofrequency (SRF) and/or laparoscopic fundoplication [57]. GORD is a common comorbidity in patients with bronchiectasis and has a variety of clinical presentations. Our index of suspicion should remain high, particularly in patients with severe disease or where conventional bronchiectasis management has failed. Identifying GORD in these patients may have important therapeutic and prognostic implications, allowing targeted treatment that may hinder progression of the disease.

10.4 Autoimmune Diseases

10.4.1 Connective Tissue Diseases

The association between bronchiectasis and autoimmune disease is well recognised, with the largest body of data available in RA. Reports describe a prevalence of bronchiectasis of up to 50% in RA, but whether this represents clinically significant or asymptomatic disease remains undetermined [58]. Compared to patients

with RA alone, RA patients with bronchiectasis have higher indices of RA activity, e.g. disease activity scores (DAS-28) demonstrating worse rheumatoid arthritis and higher levels of RA seropositivity, suggesting that the pathophysiology of these conditions maybe interlinked [59, 60].

How the two conditions are related and how one develops in the context of the other are yet to be fully determined. Three mechanisms have been considered:

1. Bronchiectasis gives rise to the development of rheumatoid arthritis—The initial event may be recurrent antigen stimulation from recurrent lower respiratory tract infections, and the immunopathological sequence of events that follows leads to the development of a multisystem inflammatory disorder with a predilection for arthropathy. Recent work suggests that RA-related autoimmunity is initiated outside the joint, in sites such as the lung, and that the chronic bronchial sepsis in antecedent bronchiectasis may induce autoimmunity, supported by the increased prevalence of positive RF and anti-CCP found in bronchiectasis patients [61]. The frequency of an abnormal cystic fibrosis transmembrane conductance regulator (CFTR) mutation DF508 present in CF was increased in patients with bronchiectasis and RA (15%) relative to patients with RA without bronchiectasis (0%) and normal controls (3%) [62]. Those with the mutation demonstrated more frequent sinusitis, lower nasal potential differences and a trend towards more severe lower respiratory tract disease, while there was no relationship to the severity of articular features. It has also been proposed that changes in the oral, gut and lung microbiome may influence autoimmunity and the structural integrity of the airway, thus leading to bronchiectasis.
2. Bronchiectasis arises from the immunosuppression associated with rheumatoid arthritis itself and/or its extensive range of immunosuppressive treatments.
3. Other diagnoses and/or comorbid conditions drive the development of rheumatoid arthritis or bronchiectasis. Systemic inflammation or immune dysregulation have been proposed as potential mechanistic pathways relating bronchiectasis with other diagnoses and/or comorbid conditions, in part due to the ageing process, which is strongly associated with an increased likelihood of developing multiple chronic conditions. RA and bronchiectasis have both been associated with excess cardiovascular mortality which may be an underpinning mechanism for excess mortality with additive cardiovascular risk arising from each pro-inflammatory comorbidity [63, 64]. It is also possible that the treatments used for RA may impact on survival.

The presence of bronchiectasis with RA carries a significantly worse prognosis. In 1997, a single-centre case-control study of 64 patients reported that patients with both bronchiectasis and RA had greatly elevated standardised mortality ratios 7.3 times higher than the general population, 5 times that of patients with RA alone and 2.4 times that of patients with BR over 5 years [65]. More recently, two large multicentre studies of 986 and 1716 patients found the presence of RA in bronchiectasis to be associated with a doubling of mortality compared to patients with bronchiectasis from other causes, supporting the premise that these patients are at higher risk

of death and that closer working with rheumatology colleagues is therefore needed [43, 66]. Sjögren's syndrome, systemic lupus erythematosus and other connective tissue diseases (CTDs) are also complicated by bronchiectasis which, if severe, may influence the decision against use of a TNF-α inhibitor for the underlying CTD.

10.4.2 Inflammatory Bowel Diseases

Repeated respiratory tract infections and bronchiectasis have frequently been noted in patients with inflammatory bowel disease, most often in those with chronic ulcerative colitis [67]. The bronchi and bowel share a common embryologic ancestry which may account for co-involvement in the same disease process. Postulated mechanisms include the infiltration of the airway by immune effector cells, enhanced autoimmune activity as part of the underlying disease and complications of immune-modulating therapies. The association could also be related to a common immunity between the lung and bowel, with the epithelial lining of both organs being exposed to common antigens in the environment, or that epithelial antigens share similarities at both sites [68]. Discussions as to whether bronchial-associated lymphoid tissue and gut-associated lymphoid tissue are distinct or partly interrelated immune systems have yet to be resolved, but both IgA producing B cells and T cells are believed to migrate from the gut to the lung. Thus, if IBD is related to an excessive immune response to a bacterial antigen, the immune cells may well be represented in the lung. Reactions against self-antigens or the same bacterial antigen being inhaled may lead to inflammatory damage at both sites [69]. Neutrophil infiltration is often implicated in the pathogenesis of the tissue destruction of both ulcerative colitis and Crohn's disease, and of course, the same has been true in bronchiectasis. It remains possible therefore that primary defects in neutrophils may play a part in some of the pathogenic changes that take place at both epithelial surfaces [70].

Bronchiectasis generally tends to occur in adulthood in non-smoking IBD individuals with no history of lung disease and typically manifests with the insidious or rapid development of cough productive of variable amounts of sputum although copious bronchorrhoea has been reported in a few cases [67, 69]. In the majority of patients, the onset of respiratory symptoms occurs weeks to years after the development of clinically confirmed IBD [71]. Less often, IBD-related bronchiectasis predates the onset of IBD and develops concomitantly or with parallel flare-ups of bowel and bronchial symptoms. Post-colectomy patients are not immune to the development of bronchiectasis, and bowel resection may even be a risk factor for onset and progression of severe disease [72].

10.5 Consequence of Other Parenchymal Lung Diseases

Bronchiectasis may complicate a number of interstitial lung diseases. These causes are often excluded from aetiological studies as traction bronchiectasis resulting from interstitial fibrosis pulling the airway wider, rather than damaging the

bronchial wall, is less likely to lead to bronchial suppuration. In these conditions, bronchiectasis is usually found where the fibrosis is most intense, namely, the upper lobes in sarcoidosis and chronic hypersensitivity pneumonitis and in the lower lobes in idiopathic pulmonary fibrosis, asbestosis and connective tissue-related interstitial lung disease. When it occurs alongside these conditions, it is associated with a higher incidence of infective pulmonary exacerbations and some of the management strategies used for bronchiectasis may be effective.

Conclusion

Proving a causal relationship between bronchiectasis and associated pulmonary and systemic conditions is somewhat difficult with limited scientific evidence available to date. It is clear that the prevalence of bronchiectasis exceeds that seen in the general population in a range of these conditions, many of which increase in parallel with the underlying disease severity. The most powerful evidence currently available to endorse these possible causal relationships rests on the biological plausibility of this being the case. Clearly, conditions that have their own effect on mortality are likely to have an additive effect on mortality associated with bronchiectasis resulting in a "double hit" that potentially increases the likelihood of developing further complications; however, the probability of interaction as discussed is interesting. The most plausible pathophysiological hypothesis for a causal relationship between the different diseases rests on the premise of a dysregulated immune system predisposing to chronic bronchial infection that would cause inflammation and progressive destruction of the bronchial wall. The presence of bronchiectasis can be easily diagnosed with HRCT, and it may be important to detect it early, as it has been linked to a poorer prognosis in numerous conditions and could require special therapeutic management.

Systemic inflammation has been proposed as a potential explanation of the mechanistic pathway relating bronchiectasis to these conditions, but the association between biomarkers of systemic inflammation and outcomes in bronchiectasis has not been well documented. Addressing this knowledge gap may allow us to identify pathway-specific treatment targets that could be beneficial in the treatment of multi-diseased bronchiectasis patients.

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Severity of the Disease, Site of Care and Self-Management

11

Tom M. Quinn and Adam T. Hill

11.1 A Global Evaluation of Severity in Bronchiectasis

Bronchiectasis is a chronic respiratory condition that for many patients results in daily symptoms, frequent exacerbations in the form of chest infections and a detrimental impact on quality of life. The cornerstone of bronchiectasis is abnormal dilation of the bronchi and this is visible on CT scanning of the thorax; however radiological assessment of bronchiectasis is not encompassing enough to fully assess severity [1]. There are patients with small, localised areas of abnormal bronchial dilatation who exhibit chronic infection, frequent exacerbations and significant symptomatology, and there are those with widespread changes on imaging who can be relatively asymptomatic. A global evaluation of the entire patient to assess disease severity is therefore required.

Stratifying patients into mild, moderate and severe bronchiectasis allows the clinician to assess the likely morbidity and mortality and to tailor specific treatment options to those who will derive most benefit. It may also be appropriate to discuss anticipatory care planning in those with more severe disease [2].

International scoring systems that have been validated include the Bronchiectasis Severity Index and the FACED score.

11.2 The Bronchiectasis Severity Index and the FACED Score

Assessment of disease severity in bronchiectasis is a relatively new concept, and until recently, there has not existed any validated model for assessing morbidity or mortality. In the past radiological extent of disease was used to describe severity, with radiological tubular bronchiectasis correlating to milder disease and varicose and cystic bronchiectasis representing more severe disease [3]. In reality a

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multi-parameter scoring system is likely to have higher sensitivity in predicting clinical outcomes.

11.2.1 Bronchiectasis Severity Index

The Bronchiectasis Severity Index (BSI) was primarily developed by a team working at the Royal Infirmary Edinburgh, UK, with data from a 4-year prospective cohort study (see Table 11.1). 1310 patients with stable non-CF bronchiectasis were recruited in total (including other validation centres). A diagnosis of bronchiectasis was made based on high-resolution CT images and a clinical history in keeping with the condition. The primary end points that the team assessed were mortality, hospitalisation rate, exacerbation frequency and quality of life measures [2].

The BSI assigns points based on 9 variables allowing a score to be calculated from 0 to 26 which is able to stratify patients into mild, moderate or severe disease.

The calculation is complex and so an online calculator exists (www.bronchiectasisseverity.com).

- A score of 0–4 equals mild bronchiectasis with a 4-year mortality of 0–5.3% and 4-year hospitalisation rate of 0–9.2%.
- A score of 5–8 equals moderate bronchiectasis with a 4-year mortality of 4–11.3% and 4-year hospitalisation rate of 9.9–19.4%.
- A score of nine and above equals severe bronchiectasis with a 4-year mortality of 9.9–29.2% and 4-year hospitalisation rate of 41.2–80.4%.

The variables listed above which make up the Severity Index were found to have an impact on the primary outcomes and so the overall severity of the condition. The

Table 11.1 Variables involved in calculating the severity score in the Bronchiectasis Severity Index

	Factor and points for scoring system			
Age (years)	<50 (0 points)	50–69 (2 points)	70–79 (4 points)	>80 (6 points)
BMI (Kg/m^2)	<18.5 (2 points)	18.5–25 (0 points)	26–30 (0 points)	>30 (0 points)
FEV_1% predicted	>80 (0 points)	50–80 (1 point)	30–49 (2 points)	<30 (3 points)
Hospital admission within the last 2 years	No (0 points)		Yes (5 points)	
Number of exacerbations in the previous 12 months	0 (0 points)	1–2 (0 points)	≥3 (2 points)	
MRC breathlessness score	1–3 (0 points)	4 (2 points)	5 (3 points)	
P. aeruginosa colonisation	No (0 points)		Yes (3 points)	
Colonisation with other organisms	No (0 points)		Yes (1 point)	
Radiological severity	<3 lobes affected (0 points)	≥3 lobes or cystic bronchiectasis in any lobe (1 point)		

authors then grouped the patients into mild, moderate and severe categories based on the severity score.

The BSI was supplemented in 2016 by a scoring system designed by McDonnell et al. assessing the impact comorbidities have on 5-year hospitalisation and mortality risk in those patients with bronchiectasis [4].This international cohort study analysed data from almost 1000 patients to construct the Bronchiectasis Aetiology Comorbidity Index (BACI). The various comorbidities and their associated points are:

- Metastatic malignancy – 12 points
- COPD – 5 points
- Inflammatory bowel disease – 4 points
- Iron deficiency anaemia – 3 points
- Asthma – 3 points
- Peripheral vascular disease – 3 points
- Haematological malignancy – 6 points
- Cognitive impairment – 5 points
- Chronic liver disease – 4 points
- Diabetes mellitus – 3 points
- Pulmonary hypertension – 3 points
- Ischaemic heart disease – 2 points

A cumulative score is calculated which allows patients to be grouped into low, intermediate and high risk (see Table 11.2).

Similar to the BSI, the BACI is validated to assess future risk of mortality, exacerbation and hospitalisation. The authors showed that adjusting for comorbidities strengthened the BSI score and both systems used simultaneously were superior to when used alone. An online BACI calculator can be accessed on www.bronchiectasisseverity.com.

11.2.2 FACED Score

A separate scoring system which has been validated to predict 5-year mortality in bronchiectasis is the FACED score (the acronym stands for each of the individual points of the scoring system) (see Table 11.3). FACED was first devised by a team led by Dr Martinez-Garcia [5].

Table 11.2 BACI scores and their estimated 5-year mortality and hospitalisation risk

	Calculated score	Estimated 5-year mortality (%)	Estimated 5-year risk of hospitalisation for severe exacerbation (%)
Low risk	0	3.5	11.7
Intermediate risk	1–5	11.7	14.8
High risk	≥6	34.9	36

Table 11.3 Variables involved in calculating severity in the FACED score

	Factor and points for scoring system	
FEV_1% predicted	<50 (2 points)	≥50 (0 points)
Age (years)	≤70 (0 points)	>70 (2 points)
Colonisation by *P. aeruginosa*	No (0 points)	Yes (1 point)
Radiological extension of bronchiectasis	1–2 lobes (0 points)	>2 lobes (1 point)
Modified MRC dyspnoea scale	1–2 (0 points)	III–IV (1 point)

The FACED score has been designed to predict 5-year mortality associated with bronchiectasis and is therefore not validated to assess the likelihood of hospitalisation or exacerbations. It was devised using a large retrospective observational study over 7 Spanish centres, with data from 839 adult patients with non-CF bronchiectasis.

Many indices are common to both the FACED score and the Bronchiectasis Severity Index. The FACED index will calculate a score of 0–7. A patient with a score of 0–2 equals mild severity and has a 5-year mortality of 4%. A score of 3–4 is moderate severity and has a mortality of 25%. A score of 5–7 is severe and carries a 5-year mortality of 56%. During the development of the FACED scoring system, the calculations were performed at the time of the initial diagnosis of bronchiectasis and as such are not validated for the follow-up of existing patients. It is unknown if a change in the FACED score correlates to a change in the patient's prognosis. The authors of the FACED paper did not find any statistical significance between colonisations with any microbial pathogen aside from *P. aeruginosa*. This is not in keeping with the BSI where chronic colonisation itself was found to impact on mortality, with those colonised from *P. aeruginosa* and MRSA having the highest mortality [2].

Both scoring systems were compared by Ellis et al. using 19 years of cohort study data in 74 patients who had been followed up at the Royal Brompton Hospital in London, UK. The team only compared mortality data and so were unable to comment on the other predictions included in the BSI. They found that both systems had a similar predictive power for 5-year mortality, whilst FACED was slightly superior at predicting 15-year mortality [6]. This study was limited by the relatively small cohort of patients, and further studies are needed to validate the two severity systems. In particular, the FACED needs further validation with regard to hospitalisation, exacerbation rate and quality of life.

McDonnell et al. published a large multicentre study critically appraising the two severity scoring systems using data from European patient cohorts [7]. 1612 patients from 7 specialist bronchiectasis units were included in their analysis, which found that whilst both systems demonstrated good predictive value for mortality, the FACED scoring system overestimated mortality in the more severe patients. Their analysis suggests that the true mortality rate with severe patients is 70% lower than that predicted by FACED. The BSI was noted to accurately predict outcomes across all areas including hospitalisation, exacerbations,

quality of life, lung function decline and respiratory symptoms. McDonnell et al. suggested that the FACED score be used as a predictor of mortality as opposed to a severity scoring system as it could not reliably be validated to predict relevant clinical outcomes such as exacerbations. In our opinion, impact analysis is required before the use of the BSI can be said to impact upon clinical outcomes.

11.3 E-FACED

The FACED score was updated in 1470 patients with bronchiectasis to validate its use in predicting future exacerbations whilst retaining its ability to predict future mortality [8]. E-FACED is now scored from 0 to 9 with only one variable added (at least one hospitalisation in the previous year). An answer of 'yes' has a score of two points and 'no' zero points. An E-FACED score of 0–3 is mild, 4–6 is moderate and 7–9 is severe. E-FACED ROC is 0.82 for predicting at least two exacerbations in the next 1 year, 0.87 for at least one hospitalisation in the next year, 0.87 for all-cause mortality over 5 years and 0.86 for respiratory mortality over 5 years.

11.4 Site of Care Decision

11.4.1 General Follow-Up

The literature supports that the bronchiectasis prevalence is increasing [9], although this may be due to increased awareness and the easy access to thin-section CT of the chest. It is important to have clear guidelines advising which patients can be cared for in primary care and who to refer to secondary and indeed tertiary care (see Fig. 11.1). The British Thoracic Society have issued guidance on which patients should be referred for to secondary care [10], and a similar model has proved to be successful in the management of other chronic conditions such as COPD. It is however possible that every patient with suspected bronchiectasis will be referred to secondary care for initial investigation and diagnosis with certain patients with mild disease and then discharged to primary care for ongoing management.

From bullet 2, the following groups of patients should be considered for referral and follow-up in secondary care:

- For initial diagnosis if CT scanning of the chest not available in primary care.
- Patients colonised by *P. aeruginosa* and opportunistic mycobacterium or who have grown methicillin-resistant *Staphylococcus aureus*. These groups of patients have a more rapid decline in lung function and increased mortality. In particular, those colonised with *P. aeruginosa* have more frequent exacerbations, frequent

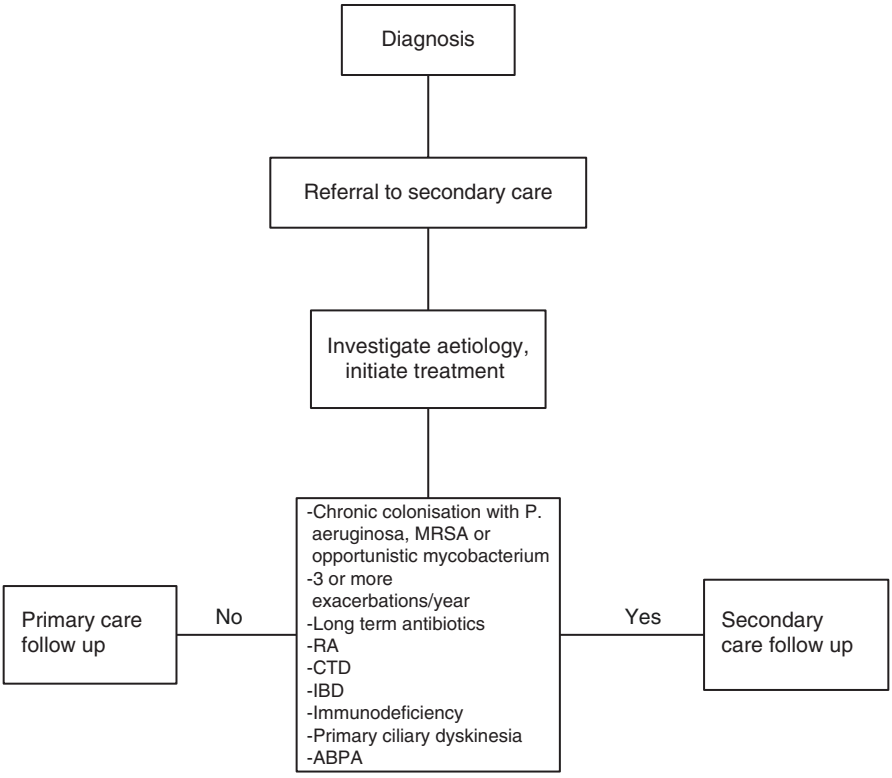

Fig. 11.1 Flow chart demonstrating approach to general management of a new diagnosis of bronchiectasis

hospitalisation and increased mortality [11, 12]. Where patients culture opportunistic mycobacterium, the treatment is complex and if given needs secondary care management.

- Patients who have suffered from numerous exacerbations a year (generally given as ≥3/year) [10]. In particular these patients should be considered for long-term antibiotics.
- Any patient who is prescribed prophylactic and long-term antibiotics (oral or nebulised) needs to be followed up in secondary care to monitor treatment response and side effects [10].
- Bronchiectasis associated with rheumatoid arthritis and connective tissue disease usually has a worse prognosis and a more complex disease [13, 14].
- Primary ciliary dyskinesia as such patients may have a more severe phenotype [15].
- Bronchiectasis associated with inflammatory bowel disease as long-term treatment is complex, often necessitating anti-inflammatory treatment.

- Bronchiectasis associated with primary immunodeficiency usually has more severe disease and requires additional treatment with immunoglobulin replacement therapy [10].
- Patients with allergic bronchopulmonary aspergillosis have a complex disease in terms of monitoring and treatment [10].

11.4.2 Acute Exacerbations

Most acute exacerbations will be adequately managed at home with oral antibiotics, usually prescribed through primary care, or the outpatient department. If possible the choice of antibiotic should be driven by previous positive sputum culture. Less frequently the patient will need admission for inpatient management. The British Thoracic Society has provided guidance on the criteria for inpatient management of an exacerbation [10]:

- Unable to cope at home
- Cyanosis or confusion
- Respiratory rate ≥25/min
- Circulatory failure
- Respiratory failure
- Temperature ≥38°C
- Unable to take oral therapy
- Intravenous therapy required after failure of oral therapy, if not able to be given at home

11.5 Self-Assessment

Self-management interventions in patients with long-term conditions include educational and behavioural components. Educational elements include disease-specific information and information about treatment strategies. Behavioural elements include goal setting and lifestyle recommendations. A number of self-management programmes are available to support and encourage patients with long-term conditions to self-manage. In the British Thoracic Society bronchiectasis guidelines in 2010, they remarked that there were at that time no published trials on the use of self-management in bronchiectasis although realistically many patients perform self-management techniques, aided by education provided by their healthcare provider. If patients are to appropriately self-manage their bronchiectasis, they need to be able to assess the severity and changes in the condition. Recognising exacerbations and deterioration is vital to early appropriate intervention. The British Thoracic Society created a self-management plan for patients with bronchiectasis with exacerbations (see Fig. 11.2).

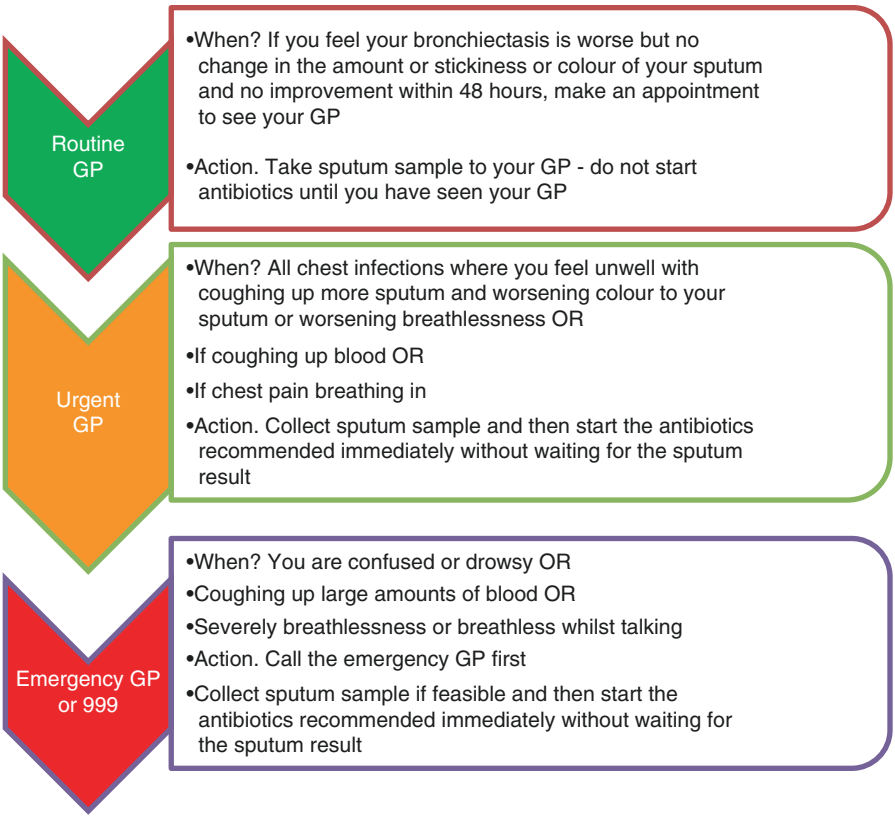

Fig. 11.2 British Thoracic Society's self-management flow chart for patients with bronchiectasis on how to manage an exacerbation (With permission from British Thoracic Society). This model exits within a UK system with close interaction between primary and secondary care

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Pseudomonas aeruginosa and Bronchiectasis

12

Anthony De Soyza and Craig Winstanley

12.1 Introduction

In this chapter, we will highlight key aspects of *Pseudomonas aeruginosa* biology and clinical challenges faced in managing infections with this pathogen. In prior chapters the microbiology of bronchiectasis has been discussed with *P. aeruginosa* noted to account for between 20 and 40% of bacterial infections in bronchiectasis. Whilst there has been a focus on *P. aeruginosa* infections in cystic fibrosis (CF)-related bronchiectasis, we will highlight the current data available in non-CF bronchiectasis, hereafter bronchiectasis [1].

12.2 *Pseudomonas aeruginosa* Biology

P. aeruginosa is a Gram-negative rod that grows readily in aerobic conditions but is a facultative anaerobe and can therefore achieve growth in the absence of oxygen, utilising nitrate as an alternative electron acceptor. This may be highly relevant within mucus plugs seen in bronchiectasis where anaerobic conditions would be expected to occur [2]. *P. aeruginosa* is a common opportunistic pathogen of humans, causing a wide range of infections [3]. In most cases, *P. aeruginosa* takes advantage when the normal defence mechanisms of the host are in some way impaired. In the context of the respiratory tract, *P. aeruginosa* can cause both acute and chronic

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airway infections [3]. However, it has perhaps been most widely studied in relation to chronic lung infections of patients with CF [4].

Understanding if certain *Pseudomonas aeruginosa* clones are responsible for infections is important. Recently whole-genome sequencing has emerged as a way of typing *P. aeruginosa*. The genomes comprise the 'core genome', which includes all genes that are common to every strain of *P. aeruginosa*, and the 'accessory genome', which can vary from one strain to another (see Fig. 12.1 [5–7]). The two most abundant clones are known as Clone C and the PA14-like lineage. Some other clones are much less prevalent, including the widely studied strain PAO1 [7–9].

12.3 *P. aeruginosa* Virulence Factors

Although classed as an opportunistic pathogen [10], *P. aeruginosa* has the capacity to produce a broad array of virulence factors that can be cell associated or secreted as extracellular products (Table 12.1) [3, 11–29].

P. aeruginosa strains produce a number of cell-associated components that play a role in the initiation of infection, through movement to target areas, or adherence to surfaces. Lipopolysaccharide (LPS) is a major component in the cell membrane of Gram-negative bacteria and plays a role in both *P. aeruginosa* adherence (via binding to asialo-GM1 receptors) and interactions with the host response (toll-like receptors) that elicit inflammatory cell activation [21].

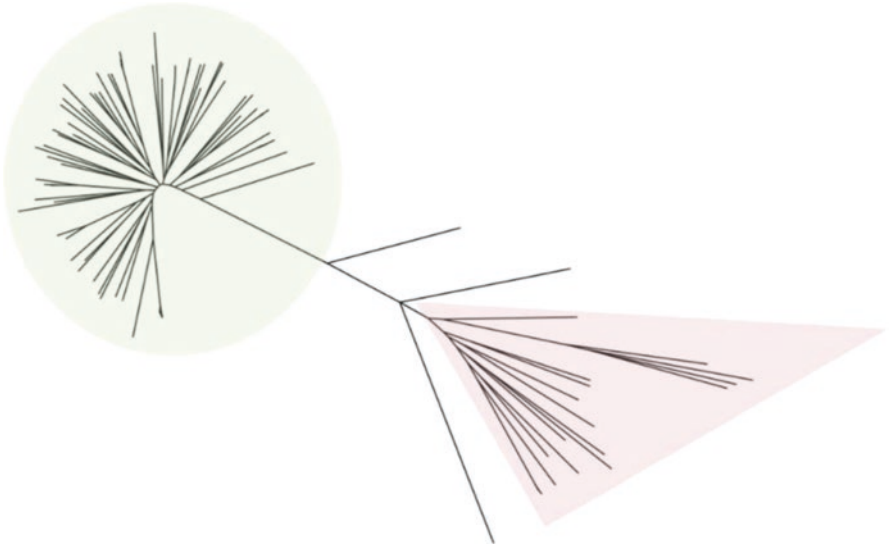

Fig. 12.1 Phylogenetic tree of multiple *P. aeruginosa* isolates, based on comparison of core genome DNA sequence data. The *figure* indicates the subdivision of the isolates into two major subgroups: I (*green shading*) and II (*pink shading*). Group I includes the widely studied strains PAO1, LESB58 and Clonce C and Group II include strain PA14. Group I is associated with exotoxin S and an invasive phenotype (the ability to invade host cells); Group II is associated with exotoxin U and a cytotoxic phenotype

Table 12.1 Virulence factors of *P. aeruginosa*

Virulence factors	Function	References
Cell associated		
Exopolysaccharides	Alginate, Pel, Psl; mucoidy and biofilm formation	[15]
Flagella	Swimming and swarming motility; promote adhesion to epithelial cells; bind to toll-like receptors	[16, 17]
Type IV pili	Twitching motility	[18, 19]
Lipopolysaccharide	Adherence and host response via binding to toll-like receptors	[20, 21]
Extracellular (secreted)		
Alkaline protease	Interferes with complement activation of neutrophils	[11]
Elastases (LasA, LasB)	Elastolytic and staphylolytic activity; role in invasion of cells	[12]
Protease IV	Protease activity targeting immunological and structural proteins	[13]
Type VI secretion	Defence against invading bacteria	[14]
Mucin sulphatase	Helps bacteria to obtain sulphur from mucin	[22]
Exotoxin A	Potent toxin from the mono-ADP-ribosyltransferase family	[23]
Phospholipase C	Targets phosphatidylcholine (PC) and sphingomyelin, lipids that make up the bulk of cellular membranes and pulmonary surfactant	[24]
Exotoxins S, T, Y, U	Effector proteins delivered via a type III secretion system; ExoS is a toxin with both GTPase-activating protein activity and ADP-ribosyltransferase activity; ExoU is a potent phospholipase capable of causing rapid cell death in eukaryotic cells; exotoxins U and S are generally mutually exclusively expressed	[25]
Pyocyanin	Redox effects on various cell functions; interaction with immune system; physical effects on cilia; defence against other microorganisms	[26]
Hydrogen cyanide	Highly toxic; irreversibly binds to the terminal oxidases of aerobic respiratory chains inhibiting aerobic respiration	[27]
Rhamnolipid	Surfactant; promotes swarming motility	[28]
Siderophores	Pyoverdine, pyochelin, secreted extracellular Fe^{3+}-chelating molecules for uptake of iron	[29]
Has and Phu	Heme uptake systems allowing uptake of iron from host hemoproteins	[29]

P. aeruginosa can secrete numerous exoproducts that contribute to pathogenicity, utilising a variety of systems, including type II, III and VI secretion systems [30–32]. The gene encoding the type II-secreted virulence factor exotoxin A is present in the vast majority of *P. aeruginosa* strains [23]. In contrast, two of the effectors secreted via the type III secretion system, exotoxin S and exotoxin U, are generally mutually exclusive. Strains producing exotoxin S are associated with the ability to invade host cells. In contrast, exotoxin U-producing strains cause host cell lysis through the action of this potent cytotoxin. These very different pathogenic behaviours could be interpreted as *P. aeruginosa* comprising two distinct 'pathotypes' [33].

Quorum sensing refers to the ability to coordinate bacterial process by cell-cell communication and is important in virulence and the formation of biofilms. Many

of the known *P. aeruginosa* secreted virulence factors are controlled by the organism's complex cell-density-dependent quorum sensing (QS) systems. These include alkaline protease, elastase, hydrogen cyanide, rhamnolipid and pyocyanin [26]. The *P. aeruginosa* QS system has a complex, comprising a QS network of two interdependent systems (LasIR and RhlIR) and two other connected systems (PQS and IQS) [34]. These systems link together in to control the secretion of virulence factors in response to population, environmental and host factors [35, 36].

Factors that are important in the early stages of infection become less important once the infection is established. There is a widely accepted concept, albeit poorly defined, of 'early' and 'late' isolates reflecting an evolution within chronic infection states. It is certainly the case that 'later' isolates from CF patients often lack the ability to produce some of the recognised virulence factors because of the accumulation of mutations (see later section on *P. aeruginosa* evolution, genetics and population structure).

Biofilms are complex extracellular matrix formation and are important factors in *P. aeruginosa* chronic infections. Bacteria in the centre of a biofilm may be in a more dormant phase and therefore protected from antibiotics and from phagocytic cells [37, 38]. *P. aeruginosa* produces three different exopolysaccharides that can contribute to biofilm formation and maturation. These are alginate, Pel and Psl [15]. Whilst there are few data available in bronchiectasis, it has been recognised for some time that alginate plays an important role in CF lung infections [39], where *P. aeruginosa* populations accumulate mucoid isolates carrying mutations that lead to overexpression of alginate.

12.4 Antimicrobial Resistance

P. aeruginosa is intrinsically resistant to many antibiotics because of a membrane that is difficult to penetrate and the presence of multiple efflux pumps. It can develop additional resistance, through mutations or the acquisition of genes via horizontal gene transfer. Resistance is most commonly acquired due to mutations that up-regulate the activity of resistance-related proteins, such as enzymes that can deactivate antibiotics (such as the Beta-lactamase AmpC [40], transport proteins that can be amended to prevent entry (porins such as OprD [41]), or efflux pump components, which function to remove antibiotics from the cell (e.g. MexAB-OprM and MexCD-OprJ) [42]. Resistance is a real-life clinical challenge in CF with 60% of isolates recently classed as multidrug resistant [43]. In contrast, whilst resistance to one or two antibiotic classes is commonly seen in bronchiectasis, multi-resistance is much rarer than CF [44].

12.5 *P. aeruginosa* in CF

P. aeruginosa is the most common and important pathogen in CF. In general, CF patients are thought to acquire their infecting strain of *P. aeruginosa* from environmental sources. Hence, different CF patients will be infected by different strains.

However, it is clear some strains of *P. aeruginosa* are transmissible between patients and hence pose a cross infection risk [45]. The most widely studied is the Liverpool epidemic strain (LES), which is the most common clone infecting UK CF patients and is associated with clinical decline. It is rarely found outside of CF [46]. The introduction of strict segregation measures, based on surveillance to identify transmissible strains using molecular techniques, can be introduced to reduce the spread of such strains in CF clinics [47–49].

12.6 *P. aeruginosa* Evolution and Adaptation in CF

P. aeruginosa undergoes evolutionary changes during chronic lung infections in CF (see Figs. 12.2 and 12.3 [50]). Phenotypic analysis of isolates obtained from patient sputum samples demonstrates the accumulation of mutants that vary in phenotypes such as colonial morphology (e.g. mucoid isolates), antimicrobial susceptibilities,

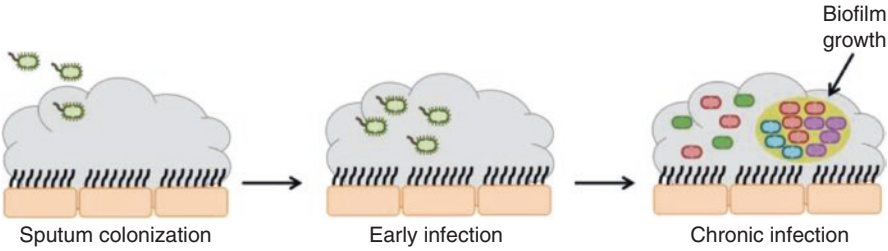

Fig. 12.2 Time course of *P. aeruginosa* infection development. (**a**) Sputum colonisation stage—*P. aeruginosa* equipped with full virulence factors enter in CF sputum; (**b**) early infection stage—*P. aeruginosa*, which exhibit the environmental or wild-phenotype species characteristics, starts its adaptation to CF environmental conditions; (**c**) chronic infection stage—*P. aeruginosa* is fully adapted to CF environment. At this stage, there is high phenotypic and genotypic diversity and formation of biofilms. After Sousa et al.

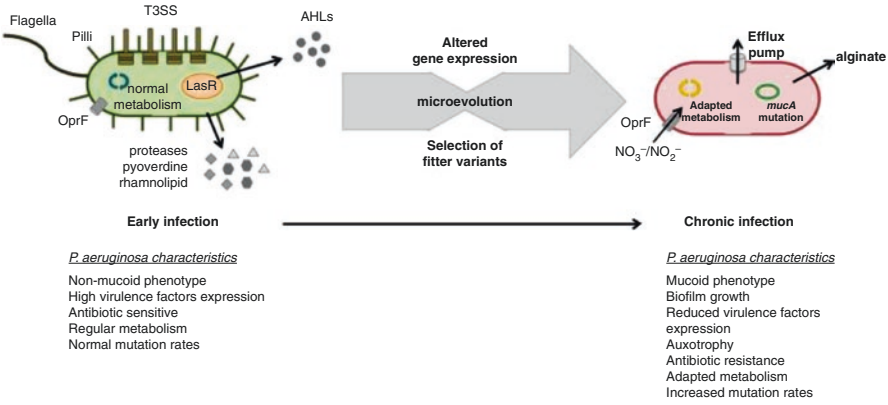

Fig. 12.3 Changes in *Pseudomonas* seen between acute and chronic infections

ability to grow on minimal media, motility characteristics and the production of virulence factors, including loss of QS-regulated factors (usually due to mutations in *lasR*), type III secreted toxins or iron scavenging systems [51–54]. The switch to mucoid phenotype, caused by overproduction of alginate (usually due to mutations in *mucA*), is considered to be a marker for the transition to chronic infection and worse outcomes [39, 55]. Interestingly, high levels of host IgG2 against alginate appear linked with poorer prognosis [56]. CF isolates also often exhibit enhanced mutation rates (hypermutability) due to mutations in mismatch repair genes (such as *mutS*) [57]. This, in turn, will increase the accumulation of mutations affecting other phenotypes, including enhanced antimicrobial resistance.

A number of studies have focussed on longitudinal collections of *P. aeruginosa* from the sputa of CF patients [58–62]. Typically, sequential isolates representing 'early' and 'late' infection stages have been compared, using whole-genome sequence analysis. These studies confirmed the tendency of *P. aeruginosa* to accumulate mutations in genes such as *lasR* (impaired QS), *mucA* (elevated alginate production) and *mutS* (elevated mutation rate). It is also common to identify mutations in global regulators, such as *lasR*, *rpoN*, *mucA*, *mexT*, *retS*, *exsD* or *ampR* [63, 64]. Changes in LPS have also been reported in 'late' CF strains with important biological effects from a switch to less inflammatory LPS structures [65, 66].

Using both phenotypic and genomic approaches, it has become apparent that populations of *P. aeruginosa* in chronic CF lung infections are heterogeneous [51–53, 67, 68]. Hence, isolates from the same sputum sample can exhibit considerable diversity with respect to important phenotypes such as antimicrobial susceptibility, and mucoid and non-mucoid variants can coexist. The analysis of explanted lungs from CF patients has demonstrated that *P. aeruginosa* communities can be regionally isolated within the lung and evolve separately [69, 70]. One consequence of this population divergence is that diagnostic microbiology practices, which often rely on the analysis of single isolates, can misrepresent the complexities of the disease state. Hence two morphologically identical colonies can give very different results when tested for antimicrobial susceptibility [54]. This is one reason why antimicrobial susceptibility testing is poorly predictive of the efficacy of antibiotics in the treatment of chronic infections [71].

12.7 *P. aeruginosa* and the CF Microbiome

Reflecting the advances in DNA sequencing, one can analyse microbial populations without the need for culture. This allows the whole microbial community (the microbiome) to be characterised [72]. Commonly 16S microbiome analysis and bioinformatics approaches are then used to infer which organisms are present and what their relative abundance is [73].

Numerous studies have demonstrated that the microbial communities in CF patients are multispecies and often contain anaerobes [74–83]. In CF, it has been shown that lower species richness (diminished diversity) in the sputum microbiome is associated with decreased lung function [75, 83] and that composition of bacterial

communities remains generally (but not invariably) stable during exacerbations, despite the fact that antibiotic therapy is applied [75, 84–87]. Because of the technology used, which targets 16S rRNA, most of these analyses have focussed on bacterial communities, but there have been studies reporting the fungal microbiome [88–90] and the virome [91].

Given the complexity of the airway microbiome, it is likely that microbial interactions play an important role in the disease processes. These interactions may be competitive (e.g. *P. aeruginosa* can attack other bacteria, such as *Staphylococcus aureus*) [92–94].

There are major gaps in our understanding of the evolutionary pressures that promote *P. aeruginosa* persistent infection and adaptation to a phenotype that worsens patient status. Whole-genome sequencing will offer insights into this, but much work is required before a fuller understanding of drivers of more rapid progression in CF emerges.

12.8 *P. aeruginosa* Epidemiology in Bronchiectasis

P. aeruginosa biology is less well described in bronchiectasis. Although it is the second most common pathogen in some bronchiectasis case series and reaches up to 40% of adult patients [44, 95–98], its prevalence is undoubtedly less common than in adult CF clinics. The burden of *P. aeruginosa* in bronchiectasis is important to contextualise. For example, in the UK there are ~11,000 affected individuals with CF [99], and therefore approximately 8000 will be infected with *P. aeruginosa* by adulthood. In contrast the burden of bronchiectasis is much higher, with over 100,000 patients affected in the UK [100]. If the 20–40% prevalence of *P. aeruginosa* in previously reported UK series [44, 95, 101] is representative of the overall UK population, then 20–40,000 patients with bronchiectasis in the UK will have persistent *P. aeruginosa* infection. Whilst there may be geographical variation in *P. aeruginosa* infections [95, 102–104] and indeed in prevalence of bronchiectasis [100, 105–107], these estimates do suggest that *P. aeruginosa* infection in bronchiectasis may be a large and unrecognised healthcare burden. Despite this there are relatively few longitudinal studies of bronchiectasis and Pseudomonas. The available data suggest that persistent *P. aeruginosa* infection is common but not invariable after first isolation in bronchiectasis [44]. Patients with less severe airflow obstruction may intermittently culture *P. aeruginosa*, but 'spontaneous clearance' appears to occur [44]. Whether patients with bronchiectasis more readily have transient only carriage of *P. aeruginosa* as compared to CF and the factors that determine persistence are however unclear. It is also unclear if these patients have persistent *P. aeruginosa* present in their microbiome but at a level that is too low to be detected by culture. Recently the fucosyltransferase 2 enzyme, encoded by the FUT2 gene, has been implicated in the susceptibility to *P. aeruginosa* infection in bronchiectasis. Non-functional enzyme resulting from a nonsense mutation in the FUT2 gene leads to a non-secretor phenotype. Those with low secretor status appeared protected against *P. aeruginosa* infection [108]. Replication studies in

other cohorts are needed, but this single-centre study raises the possibility that glycoproteins may have an important role in determining *P. aeruginosa* infection in bronchiectasis.

The available data does suggest multiple morphotypes, variation in antibiotic resistance between morphotypes, mucoidy, hypermutability and variations in in vitro virulence which have all been noted in bronchiectasis isolates [109–112]. These data give insights into methodologies on how to compare the biology of *P. aeruginosa* but are currently too limited to draw any firm conclusions on differences between CF and bronchiectasis. Studies with larger panels of isolates including multiple morphotypes and those sampled from various lung microenvironments (e.g. upper and lower lobes) are needed before we can understand if there are fundamental differences between CF and bronchiectasis isolates. Recent data has suggested bacteriophages may be important in supporting new genomic acquisition particularly in isolates from those with the greatest chronicity of infection [113]. These data also suggested the potential for bacteriophages to cross infect *P. aeruginosa* strains; this may allow genomic transfer leading to an alternative route to antimicrobial resistance [113].

Pseudomonas is important at eliciting inflammatory responses in bronchiectasis. This has been seen for interleukin-8 which drives airway neutrophilia {Chen, 2015 #3432}. Matrix metalloproteinases (MMP) that may have a role in disease progression are higher *in P. aeruginosa*-infected patients in some [114, 115] but not all studies [116]. In contrast to data describing LPS and lipid A modification in CF-derived *P. aeruginosa* [20, 117–119], there are few in bronchiectasis. Recent data has demonstrated in both CF and bronchiectasis a subset of patients may develop paradoxical 'blocking' antibodies directed against the *O*-polysaccharide of LPS that may protect the bacteria from host serum-mediated killing [120].

12.8.1 Molecular Epidemiology of *P. aeruginosa* in Bronchiectasis

There are few studies examining the molecular epidemiology of *P. aeruginosa* in bronchiectasis [121–123]. The available studies are generally small to date and are predominantly single centre. Nevertheless, these studies have suggested that bronchiectasis patients can be infected with *P. aeruginosa* clones commonly encountered in the natural environment and associated with other kinds of infection, such as the highly abundant Clone C [124]. In our single-centre work using array tube (AT) genotyping and variable number tandem repeat (VNTR) typing methods, we found no single common 'epidemic strain' when 50 isolates from 36 patients were tested [122]. The distribution of clonal types was diverse with no single dominant epidemic strain (Fig. 12.4).

Two prior studies from Spain generally using one molecular method were similarly small studies (fewer than 200 isolates studied) but generally showed the same findings [121, 123]. Larger-scale, longitudinal and multicentre studies are however clearly needed to define if and how frequently such 'CF epidemic strains' are seen in bronchiectasis patients. A recent study from the UK using whole-genome

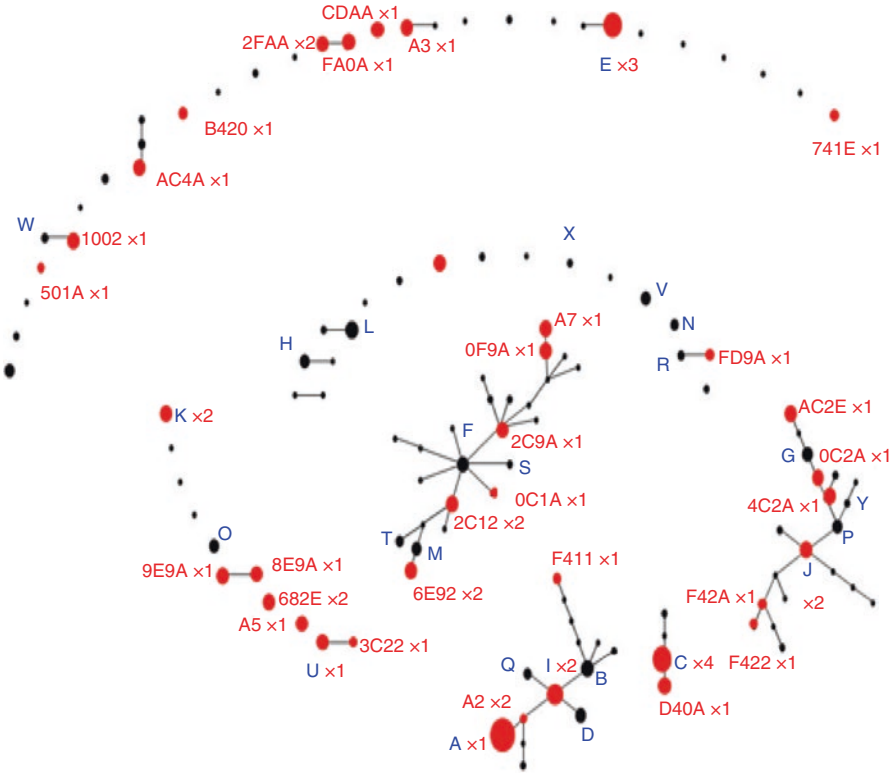

Fig. 12.4 The *figure* shows an eBURST representation of the positions of the NCFBr isolates (shown in *red*) amongst isolates from the published database of *P. aeruginosa* from multiple clinical and environmental sources. *Each dot* represents a clone based on the AT profile. The size of the dot reflects abundance within the population. *Dots connected by a line* represent a difference at one locus [SLV (single-locus variants)]. *Blue letters* indicate clone designations. Hexadecimal codes for strains without a clone designation are indicated in *red*. Also shown in *red* is the number of times that a particular genotype was found amongst the NCFBr isolates (x1, x2, x3 or x4). These are widely distributed. Data generated from De Soyza et al. [122] eburst diagram unpublished

sequencing of 189 bronchiectasis isolates has shown that highly similar strains may be shared between patients raising the possibility of transmission. In addition, this study suggests that, as in CF, *P. aeruginosa* populations in bronchiectasis both adapt by mutation and exhibit heterogeneity.

12.9 *P. aeruginosa* and the Bronchiectasis Microbiome

Metagenomics studies have confirmed the airways in bronchiectasis patients are polymicrobial [125–129]. As in CF, the bronchiectasis airway data suggests that the microbial community remains (relatively) stable during periods of exacerbation [129].

It has been suggested that a less diverse microbiome dominated by *P. aeruginosa* is associated with a future higher risk of exacerbations in bronchiectasis and higher-serum CRP and sputum interleukin-8 [128]. In addition, there appears to be evidence of mutual exclusion of *Haemophilus influenzae* from airway microbiomes rich in *P. aeruginosa* [125, 128]. Long-term macrolides, used to reduce, appear to alter the microbiome in those without *P. aeruginosa* but not in those with *P. aeruginosa* [130]. Bacterial diversity in one study was significantly positively correlated with lung function as measured by forced expiratory volume in 1 s (FEV_1). Similarly, bacterial community composition similarity correlated significantly with FEV_1, neutrophil count, and quality of life questionnaire scores suggesting a diverse microbiome was seen in more milder disease (or a more restricted core set of pathogens dominate the microbiome with increasing disease severity) [127]. Further work from the same group suggested that the bronchiectasis microbiome could predict future risk of exacerbations. The bronchiectasis airway microbiome was also associated with markers of both local pulmonary (sputum) and systemic (serum) marker of inflammation [128]. Comparative data for comparison between CF and bronchiectasis microbiomes using the same techniques are relatively few [131]. The available microbiome data confirms the culture findings that CF is more commonly associated with *P. aeruginosa* (81% positive vs 51%). Notably *P. aeruginosa* was detected by 16S rRNA sequencing in five patients with negative cultures, and two patients had more than one *Pseudomonas* spp. present based on 16S microbiome data. This suggests in both that CF and bronchiectasis patients can be infected with multiple strains of *P. aeruginosa* [131] and confirms our findings [122].

12.10 Clinical Impact of *P. aeruginosa* in BR

Persistent *P. aeruginosa* infection has been linked to poorer outcomes in bronchiectasis similar to that reported in CF [102]. These outcomes include greater levels of airway inflammation, higher morbidity, increased risks of hospitalisation and premature mortality [102, 104, 132, 133]. Increasingly *P. aeruginosa* is accepted as driving clinical deterioration: Persistent infection with *P. aeruginosa* is incorporated into clinical severity scoring systems and defines a poor prognostic group [95, 103, 134]. There is significant appetite in the clinical community for attempting 'eradication' of *P. aeruginosa* in bronchiectasis early after isolation—this is commonly practiced and has been reported as a key research priority [96, 135, 136]. Eradication therapy however is highly empiric and successful outcomes are complex to measure. The persistence of *P. aeruginosa* may be affected by the length of infection and *P. aeruginosa* adaptation/persistence responses. Hence the success of eradication therapy may be dependent on the early detection of *P. aeruginosa*, and clinical services and sampling regimens may not be sufficiently frequent and robust enough to capture very early acquisition events. Despite guidelines recommending sampling every clinic visit (British Thoracic Society [137], Spanish SEPAR [138]) in a recent consensus-finding exercise, nearly a third of clinicians only sampled sputa during exacerbations [96].

Despite the relatively high burden of *P. aeruginosa* in bronchiectasis, there are few antimicrobial resistance data. In contrast to CF, multidrug resistance and pan resistance appear much less common, with 45% of isolates resistant to at least one antibiotic but multidrug resistance rare [44]. It is unclear if this reflects an intrinsically different biology of *P. aeruginosa* in these two clinical settings or a different clinical management and intensity of antibiotic therapy driving antimicrobial resistance. Mutations associated with the resistance mechanisms described in CF isolates have also recently been identified in a whole-genome sequencing study of *P. aeruginosa* isolates from 91 bronchiectasis patients, but further confirmatory studies are still needed. The available in vitro *sensitivity tests* data suggest that the most common resistance is to quinolones, with rates of 15–20% reported, although this may reflect the reporting centre's use of ciprofloxacin as a monotherapy for milder exacerbations [44]. A variety of antimicrobial sensitivity patterns can be seen in differing isolates from the same individual. Furthermore the available data suggests the interpretation of antibiograms from a single isolate in bronchiectasis is highly variable between observers [110]. This poses significant challenges clinically in understanding which antimicrobial agent to use—in our experience patients frequently demonstrate clinical response to antibiotics initiated prior to culture data despite reported in vitro resistance. This may mirror the situation in CF; the complexities of understanding the relevance of a single isolate's sensitivity pattern in vitro may be so remote from the overall disease status as to be meaningless.

12.11 Current Management Strategies

The complexities of managing *P. aeruginosa* have been recently reviewed in a round-table discussion engaging international views and practice. It is clear there is significant variation reflecting both the evidence gaps and the differing access to therapies and clinical facilities across countries [96].

Cross infection; Infection control: To date there are no data supporting the need for mandatory segregation of patients with bronchiectasis and *P. aeruginosa* infection. It does however seem prudent to avoid significant and prolonged interaction between patients especially if they are exacerbating. It is eminently sensible that any bronchiectasis patients found to be infected with CF-epidemic *P. aeruginosa* strains should be segregated according to CF infection control guidelines [139, 140]. Centres managing CF and bronchiectasis patients often use the same clinic facilities and therefore often apply the more stringent CF cross infection protocols although there is no evidence this is effective in bronchiectasis.

Eradication therapy: *P. aeruginosa* eradication therapy is widely but inconsistently applied reflecting a lack of high-quality evidence on which patients and which regimens to use in eradication. The participants in a consensus-seeking exercise suggested commonly used regimens including oral ciprofloxacin, oral ciprofloxacin plus 3 months nebulised colistin and occasionally intravenous antibiotics [96]. The SEPAR guidelines suggest 3 weeks oral ciprofloxacin and nebulised antibiotics for 3–12 months [138], whilst the BTS note the lack of evidence and suggest 2 weeks

of oral ciprofloxacin and IV antibiotics or 3 months of nebulised antibiotics if this fails—these are however expert opinion recommendations only. Many clinicians suggest that eradication is judged by 2–3 sputum cultures negative for *P. aeruginosa* over a 12-month period [96]. A randomised trial of how to manage 'new acquisition of *P. aeruginosa*' patients has emerged as a key priority for patients and clinicians [135, 136]. It is plausible that clinicians and/or patients may decline to enter such studies if there is pre-existing evidence of more severe disease. It is also unclear when clinicians would define a cut-off distinguishing between recent acquisition of *P. aeruginosa* and when 'chronic infection' is 'established'. Current guidelines differ in this with no such definition in the BTS 2010 guidelines, whilst SEPAR guidelines define chronic infection as three or more positive cultures of *P. aeruginosa* within a 6-month period when samples are collected at least 1 month apart [137, 138]. The studies reporting eradication to date have all used various definitions [141, 142]. A standardised and internationally accepted definition would be welcome to help understand the success rates of eradication therapy.

Long-term maintenance anti-pseudomonal therapy: Management of those chronically infected with *P. aeruginosa* often focusses on suppression of bacterial load in an attempt to prolong stability or reduce exacerbation frequency. Patients selected for such therapies are suggested within BTS and SEPAR guidelines [138], usually based on both the presence of the pathogen and clinical disease burden often including recurrent exacerbations or 'higher morbidity' suggesting that long-term therapy is not to be used in culture-positive patients with low symptom burdens. The BTS guidelines suggest an exacerbation frequency of three or more exacerbations per year as a threshold for treatment escalation [137]—it is clear however that some clinicians (up to 30%) will intervene in patients with two exacerbations per year [96]. In the recent round-table discussions, 76% of respondents would use a long-term macrolide in patients with a high exacerbation frequency and persistent *P. aeruginosa* infection. This reflects there are three recent high-quality trials of long-term macrolides in bronchiectasis demonstrating a reduction in exacerbations with long-term low-dose macrolides [143–145]. These larger trials alongside a number of smaller studies have recently undergone meta-analyses [146, 147]. Each meta-analysis demonstrated the consistent effect of macrolides in exacerbation reduction and also improvement in quality of life. Infection with *P. aeruginosa* was not a prerequisite for most trials, with a range of pathogens noted in these studies. Subgroup analysis in the meta-analysis confirmed a treatment response was seen in those with *P. aeruginosa* infection. Macrolide treatment was associated with eradication of *H. influenzae* but not with *P. aeruginosa* [146, 147]. Recent data supports the role of macrolides as inhibitors of quorum sensing in bronchiectasis *P. aeruginosa* isolates.

Nebulised antimicrobials are frequently but not invariably used in those with persistent *P. aeruginosa* infection. Again, variation in practice likely reflects the limited high-quality data. One recent meta-analysis identified only eight randomised controlled trials that included 590 patients as of sufficiently high quality. These studies used a variety of antimicrobial agents including nebulised colistin, gentamicin, amikacin, tobramycin, ceftazidime and dry powder-inhaled ciprofloxacin. In

contrast to the lack of bacterial eradication seen with *P. aeruginosa*-infected patient with oral macrolides, patients in the trials were four times more likely to eradicate their baseline pathogen, including *P. aeruginosa,* with nebulised or dry powder-inhaled antibiotics [148]. Another meta-analysis limiting their analysis to long-term treatment included only 539 patients [149]. This later meta-analysis looked specifically at the eradication rate in those with *P. aeruginosa* and confirmed that according to the various eradication definitions used in the trials, there was a significant likelihood of eradication with an odds ratio of 6 for successful eradication as compared to placebo [149]. Future studies may well need to factor in better compliance monitoring beyond patient reports. It is clear however that many of the trials in bronchiectasis are not representative of the 'real-life' populations encountered with only 5–15% of patients eligible for randomisation [150].

Long-term nebulised or dry powder-inhaled antibiotics are intuitively attractive allowing high concentrations to be delivered to the site of infection. This may minimise systemic exposure and side effects. The former is important given that resistance may arise within the gut microbiome given the log fold higher bacterial load there. Irrespective of this, long-term inhalational antibiotics in bronchiectasis are likely to be associated with an increased risk of resistance—indeed emergence of a resistant population could be argued as a biomarker of compliance. The clinical implications of this resistance and the potential to minimise this by cycling alternate agents remain to be fully understood.

There are no trials comparing macrolides to nebulised antibiotics. Undoubtedly there are patient factors dictating a preference for long-term macrolide therapy over long-term nebulised therapy—these include availability within healthcare systems, ease of administration and simplicity of administration. There is also a small but appreciable rate of bronchospasm with nebulised antibiotics of ~10% [148]. In some studies however, this reaches as high as 20% in some studies with gentamicin [151]—aminoglycosides emerged in a recent meta-analysis as having a nearly fivefold increase in bronchospasm. Both the SEPAR and BTS guidelines suggest targeted therapy with nebulised drugs should be considered first line. In contrast during the recent round-table discussion, 76% of respondents stated a preference for oral macrolides as opposed to 24% preferring nebulised antibiotics [96]. There remain concerns over the resistance associated with long-term macrolides in inducing resistance and also increasing the risk of nontuberculous mycobacterium infection [96]. To date all of the antibiotics used clinically as suppression therapy, either oral macrolides or targeted nebulised, are 'off label' reflecting no specific licencing studies have been conducted in bronchiectasis in contrast to CF. A number of agents that are licenced for use in CF have 'failed' in bronchiectasis, and it is clear that the transfer of these over from CF into the management bronchiectasis has not been simple [152–156]. Many phase II trials have suggested a good microbiological response with marked fall in colony-forming units in bronchiectasis patients with each of the inhaled antibiotic agents (aztreonam, tobramycin, ciprofloxacin) progressing to phase III trials. Aztreonam solution for inhalation is effective and licenced for use in CF. However despite microbiological efficacy in phase II, nebulised aztreonam solution for inhalation failed to achieve primary

endpoints in phase III bronchiectasis studies [154]. It is likely that this failure to convert phase II microbiological efficacy into clinical benefit in bronchiectasis reflects study design and possibly clinical response differences between the two patient groups [157].

In selected patients, often those with more severe airflow limitation and high symptom burdens, clinicians will adopt cyclical intravenous antibiotics in an attempt to suppress bacterial load [158]. There are no high-quality randomised trials published in this, and local protocols are generally applied. It is again unclear if single agents or dual agent therapy regimens that include aminoglycosides are equally efficacious.

The effectiveness of suppression of microbial load with agents such as nebulised colistin, long-term macrolides or cyclical IV antibiotics is usually judged based on clinical outcomes such as reduction in exacerbation frequency or overall clinical wellbeing [153, 154, 159]. Improvements in bacterial colony-forming units or sputum purulence are rarely measured in later phase trials or in clinical practice as they are too costly and impractical. It is our own unpublished experience that sputum purulence improves rapidly with IV antibiotics, but the response is much slower with inhaled antibiotics or long-term macrolides. The recent round-table discussion identified the utility of a simple biomarker that will help define if there is a measurable treatment effect during the initiation phase of long-term suppression therapy [96].

12.12 Managing Exacerbations in Patients with Persistent *P. aeruginosa*

Patients with bronchiectasis and persistent *P. aeruginosa* infection undoubtedly have a higher exacerbation rate than those without this infection [95, 102, 103]. Whilst many patients continue to isolate *P. aeruginosa* during exacerbations, the rate and predictive factors of a new pathogen causing an exacerbation are poorly described. The management of exacerbations in a patient known to have *P. aeruginosa* when stable is often dependent on the underlying disease severity and the severity of the acute exacerbation. Many patients with milder disease or milder exacerbations will be treated with oral quinolones. In patients with mild exacerbations and prior known ciprofloxacin-resistant *P. aeruginosa*, there is limited evidence base on the best approach. In the recent round-table discussion when this scenario was presented, 15% would still try a course of oral ciprofloxacin, 11% would try co-amoxiclavulanic acid, 23% would try an acute course of azithromycin despite its poor/negligible anti-pseudomonal activity and 15% would start outpatient intravenous anti-pseudomonal antibiotics [96].

These responses may reflect a number of factors—clinicians remain unclear on the role (and accuracy) of antimicrobial sensitivity testing in chronic infections; there is an acceptance that other microbes present in the microbiome may be important in driving exacerbations perhaps indicating a clinical acceptance in the concept of polymicrobial infection with a complex microbiome in bronchiectasis.

More severe exacerbations are usually managed with intravenous antibiotics either as an in-patient or using outpatient parental antibiotics services. There remains no clear data to define dual agent therapy that includes an aminoglycoside is better to monotherapy with agents such as ceftazidime, piperacillin-tazobactam or meropenem. There are also no robust data on the optimum duration of IV antibiotic therapy—current guidelines recommend 14 days although this is expert opinion only and emerged as a key research question from patients [135].

There are a number of known unknowns that span the basic biology and pathogenesis of *P. aeruginosa* and the clinical challenges faced in managing persistent infection. Table 12.2 includes a selection of these that is not exhaustive but designed to highlight where collaborative efforts from bench to bedside may significantly advance patient care.

Table 12.2 Selected research questions in *P. aeruginosa* biology and disease management

Research question	Notes
Can biomarkers help us identify those patients at high risk of acquiring persistent *P. aeruginosa* infection?	It is possible that sputum microbiome, sputum biomarkers or human genomics can inform us of which patients are at high risk of future *P. aeruginosa* infection
What is the best way to detect 'early *P. aeruginosa*' infection?	Sputum culture is reliant on numerous patient and lab factors; sputum microbiome studies, biomarkers or breath testing may detect early infection better
In those with persistent *P. aeruginosa* infection, can we define the optimal suppression regimen that balances efficacy yet minimises resistance and side effects?	Trials of dual agent antimicrobial regimens vs. single agent antimicrobial with colony counts, longitudinal assessment of resistance and relapse/readmission rates are required
Do *P. aeruginosa* 'long-term infection' adaptation mechanisms provide a therapeutic target to prevent transition from acute to persistent infection?	The transition to persistent infection may require a variety of adaptive mechanisms and targeting these, perhaps in conjunction with conventional antimicrobials
What is the best way of antimicrobial resistance testing in managing persistent *P. aeruginosa* infection?	Sputum culture and antimicrobial testing techniques may not reflect those relevant to chronic infections with biofilm conditions. Current techniques may not reflect the antimicrobial concentrations that can be achieved by nebulised/inhaled antibiotics
Are there *P. aeruginosa* biomarkers that are predictive of successful 'eradication therapy'?	As increasing genomic data become available, can we predict treatment response from eradication therapy?
Can we develop 'in-clinic' tools that screen for *P. aeruginosa* infection and cross infection?	Current technologies are all remote from patient and still often reliant on culture: This introduces a delay between the patient contact and starting any required intervention. Rapid point of care diagnostics would reduce this delay
Does targeting other components of mixed biofilms, including other bacteria, reduce *P. aeruginosa* pathogenicity and improve clinical outcomes?	Targeting (a) acellular components of the biofilm that will allow better antibiotic penetration or (b) members of the polymicrobial community that support *P. aeruginosa* virulence may offer new therapeutic strategies

Conclusions

P. aeruginosa, undoubtedly, is an important and prevalent pathogen in both CF and bronchiectasis. We would argue that '*Pseudomonas* colonisation' appears a gross misrepresentation of the deleterious effect that persistent infection has and prefers the 'persistent infection'. In this setting increased morbidity and mortality occur. The risk factors for acquiring this pathogen and persistence of the initial infection leading to chronic persistent infection in the patients' groups all remain unclear. There is need to develop greater panels of *P. aeruginosa* isolates from multiple centres, with multiple morphotypes from the same patients longitudinally [111, 112]. Better phenotyped patient cohorts [160] with longitudinal microbiome data are also needed to understand the longitudinal risks of developing persistent *P. aeruginosa* infections [161, 162]. In those with established *P. aeruginosa* infections, there is a dearth of high-quality clinical trial data in which to define the optimal management strategies and a lack of biomarkers to define treatment response.

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The Role of Other Bacteria, Fungi, and Viruses in Bronchiectasis

13

Anne E. O'Donnell

13.1 Introduction

Bronchiectasis, a heterogeneous disease, is characterized by a vicious cycle of airway infection and inflammation that results in structural damage to the airways and the surrounding lung parenchyma [1]. Many microorganisms have been associated with bronchiectasis, both as a complication of the anatomic abnormalities and possibly as a cause of the structural disease as well [2, 3]. Diverse polymicrobial communities are present in the airways of patients with bronchiectasis [4]. Studies using standard microbiologic culture techniques have demonstrated the presence of bacterial, fungal, and viral pathogens in the lungs of bronchiectasis patients both when the patient is clinically stable and when there is an exacerbation of disease [2, 5]. Newer molecular techniques have broadened our understanding of the microbiome in bronchiectasis patients [4, 6]. *Pseudomonas aeruginosa* has been repeatedly shown to be a problematic pathogen in patients with bronchiectasis and is associated with a worse prognosis [7, 8]. Multiple epidemiologic reports have shown that approximately 20–35% of patients worldwide with bronchiectasis are chronically infected with *P. aeruginosa* [2, 9, 10]. Several antibiotic trials have been published where the main target of therapy is *Pseudomonas aeruginosa* [11–17]. (See Chap. 11 for a full review of *P. aeruginosa* infections associated with bronchiectasis.) Another problematic group of pathogens, nontuberculous mycobacteria (NTM), is a common infecting organism in bronchiectasis, particularly in the United States and in parts of Asia [2, 18]. NTM infection is fully discussed in Chap. 13. In this chapter, we will review the role of bacterial pathogens other than *P. aeruginosa* and the impact of fungal and viral infections in bronchiectasis patients. (See Table 13.1.)

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Table 13.1 Bacteriology of bronchiectasis

	Nicotra et al. [10] 1995 (n = 123)	Pasteur et al. [9] 2000 (n = 150)	King et al. [19] 2007 (n = 89)	Aksamit et al. [2] 2016 (n = 1406)
H. influenza (%)	30 (24)	35 (23)	47 (53)	116 (8)
M. catarrhalis (%)	2 (2)	20 (13)	8 (9)	20 (1)
S. pneumoniae (%)	11 (9)	13 (9)	7 (8)	49 (3)
S. aureus (%)	7 (6)	14 (9)	4 (4)	170 (12)
P. aeruginosa (%)	31 (25)	31 (21)	12 (13)	470 (33)
Mycobacteria (%)	17 (14)	0 (0)	2 (2)	657 (50)
No organism (%)	Not specified	23 (15)	21 (24)	93 (7)

13.2 General Comments

Clinical and radiographic features in bronchiectasis are generally not specific enough to predict which microbial pathogen may be present. Age and overall severity of disease have been evaluated as possible markers for specific infections but are not sufficiently specific to pinpoint the infecting organism. In one series from Israel, younger patients (less than or equal to 64 years) with bronchiectasis were shown to be more likely infected with *Haemophilus* and older patients with *Pseudomonas* and *Enterobacteriaceae* [20], but this has not been seen in other large patient cohorts. Although patients with more severe disease (based on severity scores) are more likely to have chronic *Pseudomonas* infection, other pathogens may be present and be responsible for the patient's symptoms. Radiographic patterns of disease are also not sufficiently specific for identifying the infecting organisms. Although "tree-in-bud" nodularity is frequently thought to be diagnostic of NTM infections, recent studies have shown that the "tree-in-bud" finding simply represents endobronchial inflammation not specific to a particular organism [21, 22]. Sputum color charts developed in an attempt to correlate degree of sputum purulence with specific organisms have not been reliable in predicting culture results [23, 24]. Hence, it is imperative that sputum cultures be performed in all bronchiectasis patients on a regular basis in order to target treatments and assess prognosis.

13.3 Gram-Negative Bacterial Infections (Other than *P. aeruginosa*)

The most common bacterial organism reported in many epidemiologic series is *Haemophilus influenzae*. Thirty percent or more of patients with bronchiectasis are chronically infected with *H. influenzae* [9, 10, 19]. As with all bronchiectasis patients, the cornerstone of therapy for patients infected with this organism is airway clearance by various modalities, including mechanical, pharmacologic, and exercise [25–27]. When patients infected with *H. influenzae* have exacerbations, there are multiple oral antibiotics that can be used to treat the flares of infection. Institutional specific susceptibility patterns and patient tolerance should dictate the specifics of therapy. Maintenance inhaled antibiotics are generally not recommended for patients who are chronically infected with *H. influenzae*. One study of long-term inhaled

gentamicin, which included a few patients with chronic *H. influenzae* infection, did show benefit and reasonably good tolerance [13], but studies that used maintenance aztreonam for inhalation had negative results [15]. Chronic macrolide therapy may be appropriate for frequent exacerbators as long as there is appropriate attention for potential adverse effects [28]. (See Chap. 16 for a full review of macrolide therapy.)

Other Gram-negative organisms that are occasionally isolated from patients with bronchiectasis include *Stenotrophomonas maltophilia*, *Klebsiella pneumoniae*, *Moraxella catarrhalis*, *Achromobacter*, *Alcaligenes*, *Serratia marcescens*, and *Escherichia coli*. Routine culturing of respiratory secretions is necessary in order to track the specific infecting organism in a particular patient. It is vital to target antibiotic therapy at that organism and to keep abreast of the antibiotic susceptibility pattern, which may change over time. There is insufficient data and no consensus on using maintenance antibiotics in patients infected with the above Gram-negative organisms. Expert opinion suggests that such therapy (by inhalation and targeted to the organism) may be useful in specific patients who have frequent exacerbations (greater than 2–3 per year that require systemic therapy) and/or in patients who have bothersome daily cough with a large volume of secretions. There is no specific guidance available regarding possible "eradication" therapy for Gram-negative infections with organisms other than *Pseudomonas*. (See Chap. 11 on chronic pseudomonas infections.)

13.4 Gram-Positive Infections

Staphylococcus aureus and *Streptococcus pneumoniae* are the Gram-positive organisms most frequently seen in bronchiectasis patients. In the US Bronchiectasis Registry, approximately 12% of patients had sputum cultures positive for *S. aureus* (both methicillin-susceptible and methicillin-resistant strains) and 3% for *S. pneumoniae* [2]. Treatment of patients with these infections includes the usual airway clearance modalities and targeted antibiotic treatment. There are no data available for maintenance inhaled antibiotics for patients chronically infected with Gram-positive organisms. As with Gram-negative infections, there may be a role for targeted antimicrobial suppressant therapy for patients with frequent exacerbations and/or significant and bothersome day-to-day symptoms. Chronic macrolide therapy may have a role, but worrisome resistance may develop, particularly when the infecting organism is *Streptococcus pneumoniae*. The 2010 British Thoracic Society guidelines suggest that an eradication strategy might be considered in methicillin-resistant *S. aureus* infection when the organism is first identified although this recommendation is not based on any randomized controlled trials [27].

13.5 Nontuberculous Mycobacterial Infections

Up to 60% of US patients in specialized bronchiectasis centers are infected with NTM organisms [2]. *Mycobacterium avium complex* and *Mycobacterium abscessus* are the most frequently identified organisms. Not all patients require antibiotic

therapy for these infections; the decision to treat with antibiotics should be guided by the ATS/IDSA guideline published in 2007. (See Chap. 13 for a further discussion of NTM infections in bronchiectasis.)

13.5.1 *Nocardia*/*Actinomyces*/*Streptomyces* Infections

There is little data on the frequency of these infections in patients with bronchiectasis. The US Bronchiectasis Registry reported a very small number of patients whose respiratory cultures grew *Nocardia* [2]. The decision to proceed with antibiotic treatment targeting *Nocardia* or similar species should be based on repeatedly positive cultures in the absence of another pathogen that might be responsible for the patient's symptoms.

13.6 Normal Respiratory Flora

It is not unusual for a patient with bronchiectasis to culture only "normal oropharyngeal" flora from respiratory secretions. To some extent, this may represent the limitation of routine culture techniques in identifying the infecting organism in some patients with bronchiectasis in addition to the difficulty some patients have with producing sufficient sputum for laboratory processing. One small study in 33 Greek patients with bronchiectasis sought to identify whether *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, or respiratory syncytial virus (RSV) might be present in bronchoalveolar lavage specimens; the findings were essentially negative [29]. New research into understanding the respiratory microbiome (see below) may help our understanding of what other organisms may be playing a role in the symptoms associated with bronchiectasis.

13.7 Fungal Infections

Aspergillus and *Candida* are commonly found in the respiratory secretions of patients with bronchiectasis; approximately 20% of patients in the US Registry had cultures positive for aspergillus [2]. A cohort of patient reported from Spain showed small numbers of patients had persistent culture positivity for *Aspergillus* (8.7%) and *Candida* (34.5%) [30]. It can be difficult to determine if these organisms are playing a role in the infectious symptoms or are simply bystander organisms in patients with other primary pathogens. Treatment aimed at *Aspergillus* should be considered if the patient has persistently positive cultures without another organism that might be culpable [31]. *Candida* rarely requires treatment as it is usually an oral contaminant. It is important to identify patients with the syndrome of allergic bronchopulmonary aspergillosis that can cause bronchiectasis; this immunologic disorder is distinct from secondary infection due to aspergillus.

13.8 Viral Infections

The role of viral infections in bronchiectasis is unclear with little data available on whether patients may be chronically infected with viruses or what role viruses have in triggering exacerbations. In a cohort of 119 Chinese adults with bronchiectasis, respiratory viruses were found more frequently by molecular testing from nasopharyngeal swabs and sputum samples when the patients had exacerbations of symptoms as compared to the stable state [5]. The most commonly identified viruses were *Coronavirus*, *Rhinovirus*, and *Influenza A* and *B*. RSV has also been found in bronchoalveolar lavage (BAL) specimens of patients with exacerbations of their bronchiectasis symptoms [29]. Seasonal variability of exacerbations in bronchiectasis has also been postulated to be due to viral exposure. Patients with bronchiectasis exacerbations may benefit from screening for viral infection, particularly in influenza season. Yearly vaccination against influenza is also recommended for all patients with bronchiectasis.

13.9 Future Directions

We are on the cusp of learning more about the polymicrobial communities present in the lungs of patients with bronchiectasis thanks to research on the respiratory microbiome. Studies to date have shown that aerobic and anaerobic bacteria are present in patients with stable-state bronchiectasis and when the patient is clinically exacerbated [4]. Emerging pathogens that may have a role in bronchiectasis exacerbations, including *Pandoraea* and *Ralstonia* species, have been identified [6]. The microbiome in bronchiectasis patients may vary according to the region in which the patient lives as well as due to antibiotic treatments and diet [32]. The degree of airway and systemic inflammation may be affected by the predominant bacterial taxa in the microbiome [33]. Finally, the ecology of the microbiome may be significantly affected by chronic therapies such as oral macrolides [34, 35]. We have much to learn from further investigation into the microbiome of patients with bronchiectasis which may inform treatment decisions. Though Tunney's study showed a surprising degree of stability in the microbial load and community composition before and after treatment of an exacerbation [4], Rogers et al. showed that long-term erythromycin changes the composition of the respiratory microbiota in patients with bronchiectasis [33]. Hence, close attention to the burgeoning literature on this area of investigation is needed for clinicians caring for patients with bronchiectasis.

Conclusions

Microorganisms other than *Pseudomonas* have a significant impact on patients with bronchiectasis. Our understanding of the wide spectrum of bacteria that infect these patients, including NTM, is growing. We know less about the impact of fungal and viral pathogens on the bronchiectatic lung. The impact of coinfection with multiple organisms is also poorly understood, especially with regard to which organism to target with specific antibiotic treatment. Current clinically available microbiologic

techniques do not provide a full understanding of the microbiologic diversity within the lungs of bronchiectasis patients. We may learn more from ongoing research into the lung microbiome as well as the impact of antimicrobial therapies on the balance of organisms within that microbiome. At the present time, it is imperative for clinicians to carefully monitor the microbiologic results of patients with bronchiectasis in order to provide optimal and judicious antibiotic treatments as well as to help with assessing the prognosis of the individual patient. The frequency of monitoring for each type of pathogen (routine bacterial, mycobacterial, viral, fungal) has not been clearly spelled out in existing guidelines. How sputum samples are handled (collection and processing) also varies from region to region and from laboratory to laboratory. In patients with established bronchiectasis, careful microbiologic surveillance in the stable and exacerbated states is needed. Clinicians need to be aware of local microbiologic data and need to track the results in individual patients. Close interaction with the local microbiology laboratory may also improve antibiotic stewardship for patients with bronchiectasis. Clinicians should strongly consider establishing a protocol for obtaining sputum cultures at regular intervals in their bronchiectasis patients based upon local infection patterns and overall experience with their patients. It is clear that routine bacterial and mycobacterial surveillance is needed; routine fungal cultures may or may not be of value and viral cultures are probably most worthwhile at times of exacerbation. More research is needed in this area to better standardize the role of microbiology cultures and microbiome results in improving the clinical outcomes of patients with bronchiectasis.

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NTM in Bronchiectasis

14

Michael R. Loebinger and Timothy Aksamit

14.1 Epidemiology/Prevalence

Recognition of nontuberculous mycobacterial (NTM) lung disease has substantially increased over the past 30 years and is associated by all measures with an increase in incidence and prevalence worldwide [1, 2]. While *Mycobacterium avium complex* (MAC) remains the most common of the NTM isolates causing lung disease throughout the world, there are geographic variations of other NTM species-specific lung disease differences at the inter- and intracontinental levels that are important to be aware of [3]. These differences are striking even across specific countries and states [4–6]. It is now estimated that there are nearly 200 different NTM species based on 16S rRNA gene sequencing emphasizing the importance of clinicians working closely with their laboratory colleagues to best identify and care for NTM lung disease patients. Prevalence rates of NTM lung disease have increased worldwide. Not surprisingly, prevalence rates of NTM lung disease appear to qualitatively parallel environmental NTM [7]. That is to say, despite the ubiquitous nature of NTM in the environment, geographic areas with increased NTM present appear to be associated with increased prevalence of NTM lung disease [4]. Complex relationships are nonetheless likely present linking the amount of NTM present in the general environment relative to corresponding household environments although this perspective is more speculation than based on robust data. The extent to which

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mitigation strategies in the household environment impact the occurrence and/or reinfection of NTM lung disease rates remains equally unclear [8].

The prevalence rates of NTM lung disease have been generally estimated to range between 1/100,000 and 20/100,000 population, with rates as high as >100 cases per 100,000 population noted in selected cohorts [2, 9, 10]. Moreover, NTM lung disease prevalence rates globally increase as age increases with the steepest increases in rates occurring after the fourth or fifth decades of life [10]. Interestingly, the chronicity of NTM lung infection further increases the prevalence rates relative to incidence rates of NTM lung disease and, as a result, remains an important feature of NTM lung disease epidemiologic analyses [11]. The lack of reportability has further compounded the uncertainty of more accurate assessments of prevalence rates with an international call to consider establishing NTM as a reportable disease [12, 13].

Taken together, the implications of the ubiquitous nature of NTM and an ageing population portend an expected increase in NTM lung disease in the foreseeable future globally.

14.2 Why Is NTM Lung Disease Increasing?

The question of why NTM lung disease is increasing is perhaps one of the most vexing questions to answer for patients as well as for investigators studying NTM lung disease. The presence of NTM is hardly a new species and as such has not just recently been identified in the mycobacteriology laboratory. Certainly, newer and more sensitive laboratory methods have contributed to increased isolation of NTM in respiratory secretions but the presence of clinically significant disease has undoubtedly increased as well. A clear aetiology for this increase is not evident, but contributing factors may include increased NTM in the environment from yet to be characterized selective environmental niche pressures as well as behavioural patterns of patients in residential environments including, for example, showering rather than bathing [10]. Any connection between potential changes in the amount of NTM in the environment and increased NTM lung disease prevalence rates, however, has not been investigated sufficiently to make definitive conclusions. Coupled with these environmental factors are additional potential risks of an ageing population as well as increased use of immunosuppressive agents which may further contribute to the increased rates of NTM lung disease. Given that NTM isolation may be associated with both municipal and water use, the degree to which these specific water source exposures contribute to development of NTM lung disease is uncertain. Nonetheless, tap water should not be used for cleaning respiratory equipment or for use with nasal irrigations. In fact, nosocomial outbreaks of NTM infection have frequently been associated with tap water exposure [1]. What impact overall increases in the use of antibiotics has had, if any, on potential increases of the presence of NTM in the environment has been speculated by some investigators but requires further investigations.

14.3 Susceptibility to NTM

The ubiquitous nature of NTM in the environment and yet limited numbers of patients with NTM lung disease in the general population strongly suggests that there are susceptibility risks for hosts who develop NTM lung disease. While specific information as to susceptibility factors for developing NTM lung disease is still elusive, there are specific factors that have been observed and confirmed to be important. Clearly, immunosuppressed individuals are at risk for NTM lung disease [1]. This increased risk includes those exposed to biologic therapeutics, which has been associated not only with NTM lung disease but also other organisms including fungi and tuberculosis [14]. Worth noting is the observation that inhaled corticosteroids have also been associated with the increased prevalence of NTM lung disease [15, 16]. Disseminated NTM disease is generally uncommon unless there is more profound immunosuppression such as the case for advanced HIV-related disease or inherited interleukin-12 or gamma-interferon axis defects [1]. The phenotypic presentation of peri- or postmenopausal immunocompetent women with nodular bronchiectatic NTM lung disease has been characterized as taller and thinner than their age-adjusted peers and may or may not have subtle IL-12 or gamma-interferon cellular responses [17, 18]. Increases in alpha-1-antitrypsin and CFTR mutations as well as musculoskeletal abnormalities including pectus excavatum and mitral valve prolapse have been consistently reported [17]. This group of patients has previously been characterized as Lady Windermere syndrome [19]. Disseminated NTM infection or other opportunistic infections are exceedingly rare in this group of otherwise immunocompetent patients. More recently, a multi-genetic model of host susceptibility genetic loci has advanced the knowledge of risk susceptibility and provided one more step closer to a more robust understanding of host susceptibility [20].

For those NTM lung disease patients with pre-existing structural lung disease such as COPD, bronchiectasis and other pulmonary conditions, NTM lung disease is phenotypically different than in the above predominately female peri- or postmenopausal immunocompetent patients without structural disease [21]. Rates of NTM lung disease in those with cystic fibrosis, primary ciliary dyskinesia and non-cystic fibrosis-related bronchiectasis have varied between 2% and 30% [22, 23]. The lowest rates have been observed historically in the UK with higher rates noted in North America. More recently, the relatively increased NTM exposure rate in North America has been further borne out amongst a large cohort of patients in the US Bronchiectasis Research Registry even though there was a participating centre selection bias for having a history of NTM lung disease or NTM isolated in respiratory secretions [24]. Arguably, the specific presence of bronchiectasis may enhance airway colonization of NTM and lead to progressive NTM lung disease although the chicken and egg analogy of which comes first, NTM or bronchiectasis, is far from established. In this regard, the relationship between bronchiectasis and the associated microbiome potentially represents a complex community with diversity

and interactions of organisms in the airway that may or may not favour development of NTM lung disease [25]. Further investigations are clearly needed to the relationships between NTM lung disease and bronchiectasis, or other pre-existing lung diseases.

A likely hypothesis therefore for developing NTM lung disease may involve exposure to ubiquitous environmental NTM organisms plus the presence of host susceptibility factors [26]. This two-component model might help, in part, explain the observations of apparent increased NTM lung disease involving nodular bronchiectatic or fibrocavitary NTM lung disease in patients residing in environments with more NTM. That is certainly not to say that NTM lung diseases cannot and does not occur in area of low environmental exposure as well.

Nosocomial transmission of NTM organism has been long recognized with exposure to tap water and only recently has also described involving human-to-human transmission involving *Mycobacterium massiliense* amongst cystic fibrosis patients [27–29]. The exact relationship between environment, host and organism (including virulence) factors leading to development of NTM lung disease is an area under current intense investigation worldwide.

14.4 Definition and Types of Disease

The definition of NTM lung disease has been well established by an international consensus statement and is based on criteria involving radiographic, microbiologic and, when present, NTM lung disease-attributable symptoms [1]. The microbiologic component of a diagnosis of NTM lung disease is generally based on multiple positive sputum cultures and when sputum is not available then cultures of either bronchoalveolar lavage (BAL) or biopsied lung tissue. These criteria were originally developed for the diagnosis of MAC lung disease and have been extrapolated to and applied to other forms of NTM lung disease.

It should be noted that NTM lung disease extends across a broad spectrum of presentations from disseminated disease in the immunosuppressed (e.g. advanced HIV disease, IL-12 and gamma-interferon defects, etc.), hypersensitivity pneumonitis (e.g. hot tub lung), nosocomial infection, pre-existing lung disease with or without cavitary change (e.g. COPD, bronchiectasis, etc.) and/or nodular bronchiectasis. For the purposes of this chapter and discussion, we will limit consideration of NTM lung disease to those patients with nodular bronchiectasis (Figure 14.1) and/or fibrocavitary disease (Figure 14.2). Not surprisingly, those with pre-existing lung disease are far more likely to have cavitary disease than patients with nodular bronchiectasis.

It is also worth noting that not all nodular infiltrates, often described as tree-in-bud infiltrates, on chest imaging are related to NTM lung disease but may be associated with a number of other infectious or non-infectious aetiologies [30].

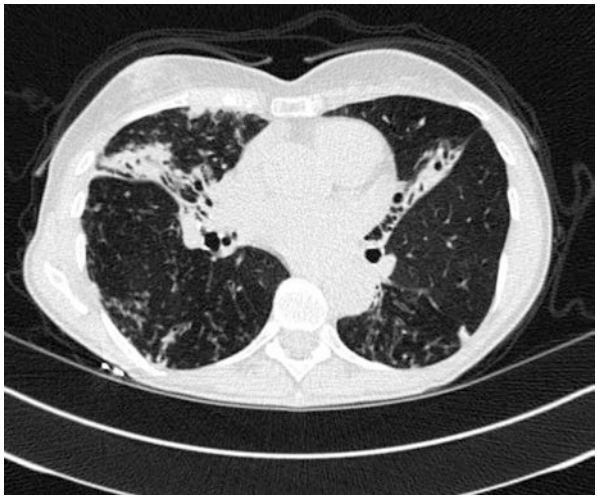

Fig. 14.1 74-year-old female non-smoker with nodular infiltrates (tree-in-bud) and bronchiectasis with predominance in mid-lung fields

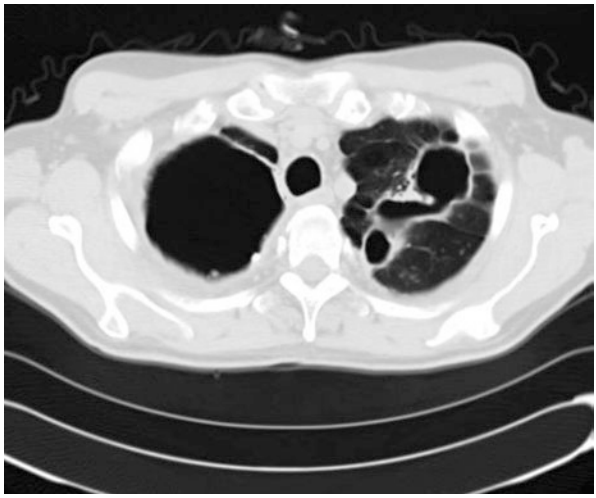

Fig. 14.2 52-year-old male heavy smoker with fibrocavitary smear-positive MAC lung disease

14.5 Who to Treat?

The answer to the question of who to treat for NTM lung disease may be even more elusive than the answer to the question of why NTM lung disease is increasing. This difficulty reflects in part the paucity of information as to the natural history of NTM lung disease with or without treatment. To a large extent the answer to this question appears to be dependent on patient phenotype and select clinical stratifying characteristics of patients most likely to experience progressive NTM lung disease. Goals of NTM lung disease treatment should include the minimization loss of lung

function, preservation of quality of life and a decrease of the morbidity and mortality associated with NTM lung disease [1]. Clearly, patients with more advanced disease including cavitary NTM lung disease and heavier disease burdens reflected in smear positivity are more likely to progress [31, 32]. This is in contrast to patients with mild nodular bronchiectatic disease that may not progress or at least minimally so without treatment for extended periods. Coupled with this variation in natural history is the understanding and experience that NTM lung disease treatment regimens involve multidrug regimens of oral, parenteral and occasionally inhaled antibiotics over prolonged periods with substantial side effects, monitoring burdens and burgeoning healthcare costs [7]. Once a diagnosis of NTM lung disease is established as outlined using an above-based strategy, the next question is generally not who to treat but whether to treat. This decision is highly individualized and requires careful participation of the patient as well as providers to assess risk-benefit ratio and agreement as to the a priori clinical goals of treatment, such as sustained sputum conversion, stabilization of progressive symptoms or radiographic changes and/or delayed loss of lung function [2]. If a decision is made not to treat the NTM lung disease, it remains critical that patients are closely followed longitudinally for progressive changes and a shift in risk-benefit ratio that would favour start of treatment at a later date.

Not all NTM isolates when detected in respiratory secretions are associated with similar risks of being clinically significant, let alone imply need for treatment [33]. Specifically, *M. gordonae* is the prototypic isolate that very rarely is associated with clinically significant disease and as rarely requires consideration for treatment. Other NTM isolates such as *M. kansasii* are at the other end of the spectrum and most often represent clinical significance warranting treatment. Likewise, many isolates, including the most common isolate, MAC, carry a degree of significance somewhere in between these two ends of the spectrum. As clinicians carrying for NTM patients, it is imperative that the treating providers familiarize themselves with this relative significance and incorporate that into the weighing of the risk-benefit ratio of whether treatment is warranted at any point in time.

Goals of treatment therefore should, in all instances, be clearly articulated a priori with patients prior to consideration of treatment. It should also be emphasized that in addition to the notion that the presence of disease does not always mean an immediate need for treatment, reinfection and recurrence rates of the original NTM species or a different NTM species are not uncommon even after a successful treatment course [1, 34]. Rates of reinfection or of recurrent infection may be more than 50% in some series. Correspondingly, radiographic changes may improve with treatment but rarely resolve completely, even in the setting of sustained sputum culture conversion. In the context of need for repeat courses of NTM therapy, it is the generally widely held experience that the first course of treatment of NTM lung disease is the most likely to have a positive microbiological, radiographic and clinical response such that selecting the timing of treatment is closely linked to the notion that the first NTM treatment course may hold the highest conversion rates relative to subsequent treatment courses [1].

Attentiveness to other diagnoses contributing to patients symptoms undoubtedly is also important and underscores the need to be mindful of contributions from bronchiectasis, gastro-oesophageal reflux disease (GERD), sinus disease, COPD and/or reactive airway disease. In many instances, nonspecific respiratory symptoms substantially improve through the treatment of other associated diagnoses even though the NTM lung disease remains present. In most, but not all, instances, once the diagnosis of NTM lung disease is established using internationally accepted definitions of NTM lung disease, the spontaneous conversion of sputum culture without treatment is unlikely to occur.

Lastly, and no less importantly, it is equally critical that once a decision to treat NTM lung disease is made, it is the responsibility of the treating providers to commit to the initiation of an accepted adequate treatment regimen to optimize benefit in so far as clinical and microbiologic response (sputum culture conversion) yet minimize potential risks of therapy. Shockingly, the degree to which prescribing providers adhere to international NTM treatment standards has been abysmal with reports of only 13% adhering to accepted regimens [35, 36]. As has been said by leading NTM investigators for many decades and initially proposed by Dr. Emanuel Wolinsky in 1979, "Proper management requires greater expertise than is needed for treatment of TB, first, to decide who needs to be treated, and second, to determine which drug regimens to use" [37].

14.6 Treatment

Treatment of NTM pulmonary disease can be difficult. The Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) [1] and British Thoracic Society (BTS) [38] have provided guidelines on recommended management strategies for pulmonary NTM treatment. These guidelines are generally based on low levels of evidence, with few randomized controlled trials having been performed in these conditions. Treatment regimens generally consist of multiple antibiotics, and treatment duration is for 1 year after successful sputum conversion. In practice, this necessitates 18 months to 2 years of therapy, but in many cases, this outcome (commonly defined by the first negative culture in a batch of three successive negatives) is never reached. Although for the most part the most common species are treated with similar drugs, there are important differences between the species, which are highlighted in the sections below.

14.7 MAC

The most common NTM associated with bronchiectasis is MAC, and there is the most data available for this species [3]. Standard treatment consists of a macrolide in combination with a rifamycin and ethambutol, with rifampicin, clarithromycin and ethambutol the most common components used in the literature to date [1]. The standardization of this treatment for MAC pulmonary disease has come from both

extrapolations of a few randomized controlled trials, in addition to data from a large cumulative number of patients from multiple, predominantly retrospective, single-site, cohort studies.

Two of the randomized controlled trials were performed in the UK with treatment of NTM patients for 2 years and a further follow-up of 3 years. The first trial included 75 MAC patients randomized to rifampicin and ethambutol or rifampicin, ethambutol and isoniazid, with the latter combination demonstrating a reduced failure or relapse rate of 16% compared to 41% ($p = 0.033$); however, there was no difference in mortality [39]. The second trial included 170 MAC patients randomized to rifampicin, ethambutol and clarithromycin or rifampicin, ethambutol and ciprofloxacin. The clarithromycin group of patients had a lower failure and relapse rate (13% vs 23%); however, no statistics were described for this comparison, and the mortality rate was higher in the clarithromycin patient group (48% vs 30%) [40]. Determining the best combination from these studies was difficult; however, the importance of the macrolide in treatment of MAC was extrapolated from early studies in HIV with disseminated MAC disease, whereby macrolide monotherapy led to clinical improvement and the development of resistance [41]. This concept has been further strengthened by studies of patients with MAC pulmonary disease. Patients with isolates resistant to macrolides have a significantly worse outlook and cure rate, as discussed below [42, 43]. The importance of macrolide sensitivity is reflected in the strong guidance to avoid macrolide monotherapy and macrolide/quinolone combinations, both of which have demonstrated an increased development of in vitro macrolide resistance [42–45]. Most guidance would also suggest consideration of stopping macrolide therapy in bronchiectasis patients taking this treatment long term for reduction in exacerbations if they have recently cultured NTM, even if the NTM do not need treatment. This relationship between clinical outcome and in vitro sensitivity has not however been demonstrated with isolates resistant to rifampicin and ethambutol, and the first UK RCT described above demonstrated that in vitro sensitivity to rifampicin and ethambutol did not impact on the treatment outcomes [39].

MAC treatment has been given both daily and three times per week, with the success of the regimen related to the severity of the NTM disease. A recent, retrospective, 217-patient study from the USA compared patients treated with daily and three times per week therapy. Outcomes were equally effective with culture conversion of 76% and 67%, respectively ($p = 0.15$) [46]. Treatment intolerance however was higher in the daily therapy group with more patients needing to alter the regimen due to side effects. Furthermore, another retrospective study demonstrated an 86% culture conversion rate in 180 patients with three times a week therapy [47]. In both of these studies, treatments were nonrandomized, and additionally all patients had less severe NTM pulmonary disease with a nodular bronchiectatic radiographic pattern without cavitation. In those with more severe, cavitary disease, the outcomes of intermittent therapy were poor, with a culture conversion rate of 4% in a randomized clinical trial assessing the impact of the addition of interferon gamma [48]. In addition to the requirement for daily therapy in those with more severe and cavitary disease, the additional use of injectable aminoglycosides should be considered at the start of NTM therapy in these patients. This is on the basis of a multicentre randomized controlled trial of 146 patients where intramuscular streptomycin and placebo were added three

times per week to daily rifampicin, ethambutol and clarithromycin [49]. The streptomycin arm demonstrated an improved sputum conversion rate (71% vs 51% $p < 0.05$). The cohort in this study included both cavitary and nodular bronchiectatic patients; however, the significant treatment burden and side effects of injectable aminoglycosides have led to recommendation for consideration of this treatment in those with more severe disease. Indeed due to the treatment-associated morbidity, aminoglycosides are often used for shorter periods to augment therapy, and studies are also investigating the use of inhaled aminoglycosides [50, 51] (see below).

14.8 *M. abscessus*

This species is predominantly associated with disease in patients with cystic fibrosis; however, its importance in non-CF bronchiectasis patients is also increasing. Literature reports are limited to case series, and most recommendations suggest an induction phase of multiple injectable agents followed by a maintenance phase of oral and nebulized antibiotics [1]. One series of 65 patients used 4 weeks of cefoxitin and amikacin followed by maintenance of oral clarithromycin, ciprofloxacin and doxycycline [52]. With this regimen, 58% of patients culture converted; however, the majority of patients with a successful outcome had a particular subspecies of *abscessus*, *massiliense* (88% converted) [53]. In those without macrolide sensitivity, either due to inducible or constitutive macrolide resistance, culture conversion was only 25% with this regimen, which is similar to the sustained culture conversion rate (19%) in a 69-patient case series from the USA [54]. Other, smaller case series have involved similar regimens but with longer durations of intravenous therapy, with a 41-patient series using intravenous amikacin for a median of 230 (60–601) days [55]. Again the outcome was better in the *massiliense* subgroup, but the overall success rate was 81% with this long-term intravenous therapy. Based on the available evidence, present treatment guidelines suggest a minimum of 4 weeks of intravenous therapy comprising 2–3 of amikacin, tigecycline, imipenem and cefoxitin in combination with an oral macrolide, followed by nebulized amikacin and 2–4 oral drugs guided by in vitro sensitivity such as a macrolide, clofazimine, linezolid, minocycline, moxifloxacin and cotrimoxazole [38].

14.9 *M. kansasii*

This species is much less commonly associated with bronchiectasis patients but may present more acutely, akin to *M. tuberculosis*. Treatment regimens are based on observational studies, the largest of which was sponsored by the BTS and documented the outcome of 173 treated with 9 months of rifampicin and ethambutol [56]. There was a single treatment failure and relapse in 15 patients where compliance was thought to be a contributing factor. Smaller studies have assessed the use of three-drug regimens with either the addition of isoniazid or macrolide to the above regimen [57–60]. In these smaller studies, relapse rates were lower with no episodes of treatment failure, and this three-drug regimen is normally recommended for treatment.

14.10 *M. malmoense* and *M. xenopi*

These species are far less common in bronchiectasis patients in comparison with MAC. *M. xenopi*, in particular, is much more common in patients with COPD. There is very little literature available on either of these species to enable evidence-based decisions on optimal treatment regimens. The UK-based randomized controlled studies performed in MAC described above also included patients with *M. malmoense* and *M. xenopi*; however, the numbers were small and conclusions hard to draw [39, 40]. There have additionally been a few noncomparator, retrospective studies with various drug regimens. Treatment recommendations are similar to those of MAC above with rifamycin, ethambutol and macrolide as the main treatment backbone. In *M. xenopi*, the largest cohort of 80 patients suggested a four-drug regimen with 41% sustained culture conversion [61], and the consideration of addition of a fourth drug (isoniazid or quinolone) is also suggested in the BTS guidelines [38].

14.11 Outcomes

Outcomes of patients with NTM relate to the species, the underlying comorbidities and the severity of the NTM-related disease. A study based in Denmark demonstrated a 5-year all-cause mortality of 40.1% for those with NTM pulmonary disease [62], which was similar to that extrapolated from the large BTS sponsored RCTs described above, where 5-year all-cause mortality rates were 38.8% MAC, 48.5% *M. malmoense* and 38.2% or *M. xenopi* [40]. There are several available retrospective studies assessing mortality rates for specific species with the largest based on 634 patients in Japan and describing a 23.9% 5-year mortality [32]. Differences in outcomes between patients treated with different regimens and those not treated are hard to compare due to the selection bias of patient groups, which is an innate limitation of these uncontrolled, retrospective studies. Some patient groups such as those with refractory disease and clarithromycin resistance have worse mortality rates with the latter demonstrating a 34% 1-year mortality rate in those that did not sputum convert in one study [45]. Mortality in these patients is often due to underlying comorbidities, and studies that have measured it have described a lower NTM-specific mortality with a rate of 5.4% MAC-specific mortality recorded in the Japanese retrospective study [32] and similar rates in the BTS RCT studies (2.9% MAC, 2.9% *M. xenopi*, 3.6% *M. malmoense*) [40], although determining accurate causes of death is likely to be very difficult.

14.12 Refractory Disease

Refractory disease describes persistently positive sputum cultures despite treatment regimens described above. Different studies have suggested failure of sputum conversion at 6 months or 12 months to define refractory disease [1, 50, 51, 63–65]. The

success rate of sputum conversion has varied significantly in the literature. In MAC lung disease, success rates have been reported as high as 86% sputum conversion in a large study of those with the nodular bronchiectatic form [47]; however, an RCT described a success rate of 5% in those with fibrocavitary MAC on a similar 3x per week regimen [48]. Once the NTM lung disease has become refractory based on persistent culture positivity, options are limited and outcomes in refractory disease are poor [66]. Retesting in vitro sensitivity patterns may be important, particularly to assess for the development of macrolide resistance. Common practice is to alter the NTM treatment regimens by adding or substituting drugs based on in vitro sensitivity [65]; however, some studies have demonstrated no improvement in outcome with this approach but an increase in the treatment-related side effects [63]. As noted previously, most of the available data relates to MAC lung disease. Specific studies have tried adding moxifloxacin to patients with refractory MAC with a retrospective, uncontrolled study demonstrating culture conversion in 12/41 previously refractory patients [64]. However other retrospective studies have suggested no improvement with the addition of a quinolone in MAC-resistant patients [67]. A recent phase 2 study in patients with refractory MAC or *M. abscessus* added liposomal nebulized amikacin to the previous regimen or placebo in 89 patients. This study did not meet the primary endpoint of a reduction in semi-quantitative microbiological score; however, a significant number of patients on the active drug became sputum negative, and in many cases, this was sustained [51]. The addition of this liposomal inhaled amikacin to a failed regimen for MAC has been the subject of a larger phase 3 multicentre trial with the results hopefully available in the near future. Surgery may have some role in refractory disease with certain disease patterns, such as unilateral cavitary disease. Case series have reported good outcomes including groups of refractory patients [68]. In retrospective studies on treatment of macrolide-resistant MAC cases, the best outcomes based on sputum conversion and survival have been shown with combinations of surgery and intravenous aminoglycoside [45, 67]. Patient selection is however very important as surgical morbidity including bronchopleural fistulae can be significant [68].

14.13 Future Agents

Present treatment options for NTM lung disease are suboptimal, and there is a clear unmet need for new drugs and regimens. There may be some role for liposomal nebulised amikacin, as described above, in refractory disease, but perhaps also a potential role within initial therapy paradigms for some patients. New drugs have recently come to the market for drug-resistant TB that may hold some promise in NTM disease. Bedaquiline is an antibiotic that affects the proton pump for ATP synthase. A small study was performed in the USA with the addition of bedaquiline to NTM treatment in ten (six MAC, four *M. abscessus*) patients with refractory NTM, selected on the basis of the insurance company willing to pay for the drug [69]. Although nine patients had symptomatic improvement, radiological changes were variable. There were some transient but unmaintained negative cultures over

the 6-month period. Another new TB medication, delamanid, has poor in vitro sensitivity to most NTM; however, there are a few compounds presently on the TB treatment pipeline that have more promising in vitro sensitivity profiles that may provide further opportunities in the future [70]. Other drugs such as linezolid and clofazimine are also being used more commonly in practice for difficult NTM disease. Linezolid was demonstrated to be tolerable over a prolonged period in NTM patients in one study; however, efficacy was not assessed [71]. Clofazimine has been shown to have some in vitro synergy with amikacin [72], and a Canadian retrospective study has demonstrated good outcomes with the use of clofazimine as an alternative to rifampicin in standard MAC treatment regimens [73]. Avibactam is a betalactamase inhibitor that may also have some activity in combination against abscessus [74]. Immunomodulatory drugs such as interferon gamma are not presently recommended, but are perhaps something that would be worthwhile looking at again in the future. An RCT with inhaled interferon gamma in addition to standard 3x per week MAC therapy in 91 patients was terminated early after the interim analysis demonstrated no effect based on culture, radiology or symptoms [48]. A further Cuban study of patients added intramuscular interferon gamma or placebo to a standard treatment regimen and demonstrated an improvement in numbers with "complete response" with the active drug; however, the numbers were small, and the definition of response and the "standard" therapy were both unconventional [75].

14.14 Summary

NTM is common in patients with bronchiectasis with more than 10% of patients affected. Determining the contribution of NTM to the clinical and radiographic changes in patients with bronchiectasis can be difficult and impact on assessment, monitoring and determining the need for treatment. The situation can be further complicated by the use of macrolide monotherapy in bronchiectasis. Macrolides have been shown to improve clinical outcomes in some bronchiectasis patients; however, macrolide monotherapy in patients with NTM disease is contraindicated. Determining who to treat, with what and for how long remains a difficult question that requires a more robust evidence base going forward.

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Exacerbation of Bronchiectasis

15

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15.1 Introduction: Role of Exacerbations in Bronchiectasis

Bronchiectasis is a heterogeneous chronic respiratory disease that is characterized by frequent respiratory infections. In fact, both acute and chronic respiratory infections are considered typical determinants of the natural history of bronchiectasis, and they strongly predict patients' quality of life and disease progression. In general, it is common belief that most of the exacerbations of bronchiectasis in adults are infectious events.

The role of exacerbations is so important that many authors define bronchiectasis as a syndrome characterized by permanent bronchial dilatation and recurrent respiratory infections (exacerbations). In addition, the pathophysiological theory of "Cole's vicious cycle," which explains the development of bronchiectasis, is based on an initial infectious episode that triggers the local inflammatory response and permanent bronchial damage. As a result of the vicious cycle, patients with bronchiectasis usually suffer from chronic airway inflammation, functional limitation (fatigue, dyspnea), and recurrent acute infections (exacerbations) or chronic airway infections.

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Various studies have shown that an increased frequency of exacerbations is associated with increased airway and systemic inflammation, [1] and progressive lung damage [2, 3]. In addition, more severe (i.e., requiring hospitalization) and more frequent exacerbations (>2/year) are associated with a worsened quality of life, daily symptoms [4], lung function decline [5], and mortality [3].

Consequently, the prognostic score most used in bronchiectasis—the Bronchiectasis Severity Index—includes both exacerbations and hospitalizations (more severe exacerbations) between the nine determinants for disease severity assessment [3]. The FACED score (FEV1, Age, Chronic colonization, Extension, Dyspnoea), the alternative prognostic score for mortality risk, has recently been updated to include the exacerbations as a relevant determinant of the risk of mortality and future exacerbations [6–8].

As a result, most of the therapeutic interventions suggested in bronchiectasis and the most relevant clinical trials, are directed at preventing exacerbations or reducing their frequency and severity [9, 10]. For instance, influenza and pneumococcal vaccines, continual use of macrolides and inhaled antibiotics, and respiratory physiotherapy, are all aimed at minimizing the impact of exacerbations on patients' quality of life and disease progression [9–13]. In particular, the threshold of three or more exacerbations per year is usually considered to classify patients with unstable clinical conditions who should be considered for continuous (inhaled or oral) antibiotics [9].

Taking all these factors into consideration, it is clear that identification, treatment, and prevention of exacerbation is crucial in the management of bronchiectasis. In line with this, the most recent and relevant clinical trials of inhaled antibiotics use "time to first exacerbation" or "the mean/median number of exacerbations" as primary outcomes [14, 15].

15.2 Definition

Numerous definitions have been given so far to define exacerbations of bronchiectasis.

Most of them include an acute change in cough, sputum (color, viscosity, and volume), and a number of additional symptoms, such as increased dyspnea, wheezing, fatigue, malaise, thoracic pain, spirometric and oxygenation worsening, hemoptysis, fever, etc. Many studies have included in their definitions of exacerbation the need for antibiotic therapy according to the decision of the attending physician. This criterion is frequently controversial, because (1) it assumes that only bacterial infections are the real cause of exacerbations, and (2) the administration of antibiotics should be a consequence of the definition, and not part of it. More recently, during the First World Bronchiectasis Congress held in Hanover in July 2016, an international (from Europe [EMBARC], the USA, Australasia, and South Africa) task force of 28 experts in bronchiectasis generated an agreed-upon definition of exacerbations of bronchiectasis [16]. Firstly, a review of exacerbations used in clinical trials between 2000 and 2015 was performed [1, 11–14, 17–31]. Secondly, a Delphi

process [32], followed by a round table discussion, was used to identify the most relevant elements to include in a definition of exacerbations and to achieve a final agreement on it. Finally, the definition proposed included a deterioration in three or more of the following key symptoms, for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; hemoptysis, and a clinician who determines that a change in bronchiectasis treatment is required (Table 15.1).

It is possible that in the future, the need to grade severity of exacerbations will emerge as a useful clinical tool to decide on appropriate therapy and diagnostic tests (as for pneumonia). At the moment, only the Spanish guidelines provide a definition of severe exacerbation in the presence of any of these factors: tachypnea; acute respiratory failure; exacerbated chronic respiratory failure; a significant decline in SaO_2, respiratory function, or hypercapnia; fever of more than 38°C; hemoptysis; hemodynamic instability; or impaired cognitive function [10]. More recently, the updated version of Spanish guidelines introduced the concept of "very severe exacerbations" when characterized by hemodynamic instability, altered mental status, or the need to be admitted to an intensive or intermediate care unit (Table 15.2, Martinez-Garcia et al. Arch of Broncopneumol. Ahead of print).

Table 15.1 Definition of exacerbation of bronchiectasis according to Pulmonary Exacerbation in Adults with Bronchiectasis: A Consensus Definition for Clinical Research. (Hill et al, ERJ ahead of print. ERJ-00051-2017.R1)

Exacerbation of bronchiectasis: a deterioration in three or more of the following key symptoms for at least 48 h	1. Cough 2. Sputum volume and/or consistency; sputum purulence 3. Breathlessness and/or exercise tolerance 4. Fatigue and/or malaise 5. Hemoptysis
In addition, a clinician must determine that a change in bronchiectasis treatment is required.	

Table 15.2 Definition of severe exacerbations of bronchiectasis according to SEPAR Guidelines 2017. (Martinez-Garcia et al. Arch of Broncopneumol. Ahead of print)

Severe exacerbation	
Presence of any of these factors	1. Tachypnea 2. Acute respiratory failure 3. Exacerbated chronic respiratory failure 4. A significant decline in SaO_2 or respiratory function or hypercapnia 5. Fever of more than 38°C 6. Hemoptysis
Very severe exacerbations	
Presence of any of these factors	1. Hemodynamic instability 2. Altered mental status 3. Need for admission to an intensive or intermediate care unit

15.3 Epidemiology of Exacerbations

Although various studies in the 1980s and 1990s suggested a frequency of exacerbations greater than four events/year [33–38], more recent data from the European Bronchiectasis Registry (EMBARC) [39] have shown that the majority of patients suffer two exacerbations/year. Likely, a serious referral bias of sicker patients to more specialized centers was responsible for overestimating the frequency of exacerbations.

However, it is worth mentioning that >45% of all patients might have more than two exacerbations year, and it is has been reported that one-fourth of all BE patients might be responsible for 80% of the total costs of the disease [40]. In addition, various authors have described an increasing trend in the number of hospitalizations due to bronchiectasis [41, 42]. In particular, in Germany, an increasing rate of hospitalizations has been reported in the last decade [41]. It is possible that the increased awareness of the disease—such as the improved availability of diagnostic tools (high-resolution CT scan) have contributed to better identification of bronchiectasis patients and their exacerbations.

Interestingly, some researchers have written that bronchiectasis exacerbations may require a mean length of hospital stay (LOS) in the United Kingdom of 10 days, which is longer than that required for COPD [43], while another publication from the USA describes a mean stay of 6 days [44]. However, we realize that factors such as local healthcare organization and other socio-economic aspects can highly influence this outcome. For this reason, it is very difficult to evaluate the economic burden of the disease by measuring the mean length of stay through LOS.

Otherwise, De la Rosa et al have clearly identified the frequency of exacerbations as one of the main determinants of the economic burden of bronchiectasis in more advanced patients (high FACED score) [45]. Apart from the economic problem, exacerbations can also negatively influence prognosis. In fact, various longitudinal studies have described a considerable increase in mortality risk after an exacerbation of bronchiectasis, particularly in the subset of patients with comorbid chronic obstructive pulmonary disease (COPD) [39, 44, 46, 47].

15.4 Risk Factors

Despite the fact that the etiology of exacerbations is not always clear (bacteria, virus), the factors associated with an increased risk of suffering an exacerbation of bronchiectasis are well described. A broad radiological extension (>2 lobes, bilateral), a cystic aspect, a moderate to severe BSI score, and a history of recurrent exacerbations in the last year—are clear predictors of further exacerbations [3, 48]. In particular, the BSI score was developed according to the analysis of risk factors for hospitalizations (severe exacerbations needing hospitalization) [3]. Independent predictors of future hospitalization included prior hospital admissions; severe dyspnea; FEV_1 < 30% predicted; *Pseudomonas aeruginosa* colonization; colonization with other pathogenic organisms; and three or more lobes with bronchiectasis. Two

recent prognostic scores have incorporated exacerbations into the original FACED score; both E-FACED and Exa-FACED scores showed better prognostic capacity and improved risk classification [7, 8].

A chronic infection by *P. aeruginosa* is associated with an increased risk of hospitalization [49, 50] and, in the long run, of mortality [51]. However, McDonnell et al. also showed that chronic airway infections by *Haemophilus influenzae* have increased outpatient morbidity due to frequent exacerbations not requiring hospitalization [49].

A good model of risk stratification based on the airway microbiome analysis in stable clinical conditions was proposed by Rogers and colleagues [52]. The microbiome analysis on induced sputum from 107 adult patients identified three main groups: *P. aeruginosa*-dominated, *H. influenza*-dominated, and other taxa-dominated. Although both *P. aeruginosa* and *H. influenzae* were characterized by poorer lung function, as well as increased systemic and airway inflammation, only *P. aeruginosa* was finally associated with higher exacerbations frequency.

As a confirmation, Aliberti et al. identified a specific "*Pseudomonas*" clinical phenotype through a cluster analysis based on demographics, comorbidities, and clinical, radiological, functional, and microbiological data [4]. Patients with chronic *P. aeruginosa* showed significant differences in terms of quality of life, exacerbations, hospitalizations, and mortality during follow-up compared with "other chronic infection," "daily sputum," and "dry bronchiectasis" patients [4].

A Chinese group has developed a specific score to identify patients with bronchiectasis at risk of exacerbations, including: *P. aeruginosa* colonization (OR = 3.227), ≥3 affected lobes at HRCT scan (OR = 3.179), prior ICU admissions (OR = 2.499), and FEV_1 < 50% predicted (OR = 2.497) [53]. A broader external validation of this score would be helpful to integrate it into clinical practice.

The coexistence of COPD or asthma in bronchiectasis patients has been widely recognized to increase the risk of exacerbations [47, 54]. In particular, a meta-analysis of COPD patients showing bronchiectasis on CT scans has described a clear increase in the exacerbation risk [55]. In asthmatic patients, the association with bronchiectasis has been described only for severe patients [56, 57] in whom obstruction severity seems to be associated with the risk of BE, but its predictive value is poor [57].

This association between asthma and bronchiectasis is more frequent in the presence of *Aspergillus* sensitivation [56] or in the case of neutrophilic inflammation [57], which is described usually only in a minority of asthma patients and seems to be associated with an increased exacerbation risk [54]. However, the scarce literature on this clinical association requires further investigation in order to define clinical outcomes of this subset of bronchiectasis population.

Interestingly, a British study of adult bronchiectasis patients also identified airway reflux as independently associated with an increased risk of ≥3 bronchiectasis exacerbations in 1 year [58]. Although gastro-esophageal reflux has been reported as a potential etiology of bronchiectasis, its association with the disease has never been completely shown; similarly, it is not clear whether airway reflux can be a real causative factor of exacerbations, or simply a marker of associated conditions.

Another factor to consider in terms of risks of exacerbations is nutritional status. It is well known that the immune response of the general population is highly influenced by nutritional status [59]. Although the relationship with body mass index (BMI) is not as strong as for cystic fibrosis [60], long-term survival of bronchiectasis patients seems to be influenced by BMI [61]. Chalmers et al have described an association between Vitamin D deficiency and the risk of exacerbations and chronic infections [62]. In addition, a BMI $\leq$ 18.5 Kg/m^2 has been associated with an increased mortality risk in bronchiectasis [3].

Lastly, it has been reported in some regions that socio-economic factors can also influence the risk of exacerbations in both children and adult populations [63, 64] (Table 15.3).

15.5 Etiology of Exacerbations

As for all chronic respiratory diseases, the knowledge of the etiology of exacerbations of bronchiectasis is a crucial factor. In fact, due to the high impact of exacerbations on quality of life and long-term prognosis for bronchiectasis, the understanding of pathophysiology of these events can surely improve management of the disease.

In general, it is assumed that all exacerbations are due to infections, although there is probably no sufficient scientific evidence to identify exacerbations due to other causes, such as treatment incompliance or pulmonary embolism, as in COPD [65]. In addition, it is difficult to distinguish between bacterial, viral, and, more rarely, fungal exacerbations from clinical presentation and analytical data.

Recently, Rosales et al. have identified *P. aeruginosa, respiratory viruses, Staphylococcus aureus, Streptococcus pneumoniae, H. influenzae and Moraxella*

Table 15.3 Risk factors for exacerbations of bronchiectasis

Risk factor	Source
Cystic bronchiectasis	Kadowaki et al. [48]
≥3 lobes affected by bronchiectasis at CT scan	Chalmers et al. [3]
FEV_1% pred. <30–50%	Chalmers et al. [3]
	Li et al. [53]
Chronic airway infection by *Pseudomonas aeruginosa*	Chalmers et al. [3]
Chronic airway infection by *Haemophilus influenzae*	McDonnell et al. [49]
≥3 exacerbations during the previous year	Chalmers et al. [3]
COPD	Du et al. [55]
	Goeminne et al. [47]
Severe asthma	Menzies et al. [56]
	Gupta et al. [57]
	Mao et al. [54]
Airway reflux	Mandal et al. [58]
Nutritional status	Qi et al. [61]
	Chalmers et al. [1]
Socio-economic factors	Roberts et al. [64]

catharrhalis as the most frequent microorganisms in sputum cultures or nasopharyngeal swabs (PCR analysis of viruses) of exacerbated patients [66]. In contrast, atypical bacteria seem to be very infrequent in this population [66, 67]. However, patients suffering pneumonia showed *S. pneumoniae* to be the most frequent isolate, irrespective of previous airway chronic infection [66].

The same study identified a polymicrobial infection in more than 35% of all cases of exacerbations (both pneumonic and non-pneumonic): two bacteria were identified in16% of pneumonia cases and 13% of non-pneumonic exacerbations, while a combination of bacteria and virus was found in 22% and 11% of cases, respectively. Lastly, in 12% and 8% of cases, a fungal isolate was found in association with a bacteria [66].

The role of viral infections during exacerbations of bronchiectasis has also been confirmed in previous studies in 25–50% of both adult and children's populations [68, 69]. Similar data have also been reported for CF [70] and COPD [71]. The most frequent viruses described in exacerbated bronchiectasis are coronavirus, rhinovirus, influenza virus (A and B), metapneumovirus, respiratory syncytial virus, and parainfluenza 3 [66, 68, 69].

However, the mechanisms of virus-induced bronchiectasis exacerbation need to be further investigated. In fact, a human model of rhinovirus infection has been shown to be able to impair IFN production and neutrophilic inflammation, and trigger a COPD exacerbation through inflammatory mechanisms [72], or by inducing a secondary bacterial infection [73]. These pathophysiological patterns have not been clearly demonstrated in bronchiectasis but they are likely, considering the fact that, like in COPD, airway inflammation is neutrophilic.

In addition, in COPD, increased bacterial concentration due to the acquisition of a new strain of chronic *H. influenzae* has been described as a cause of exacerbations [74]. Unfortunately, there is no information to support this theory in bronchiectasis, but a change in the host-pathogen interaction could also be hypothesized during exacerbations on the base of current evidence on microbiome, classical microbiology, and inflammatory patterns [67–69]. In fact, Tunney et al. investigated the lung microbiome in bronchiectasis patients and surprisingly found no significant differences between stable conditions and exacerbations [75].

In line with this hypothesis, Brill et al. prefer to define bronchiectasis exacerbations of non-CF bronchiectasis as inflammatory events, with worsened symptoms, lung function, and health status [76]. Nonetheless, we have clear scientific evidence of the association between antibiotic administration and a consequent drop in bacterial load and systemic and local inflammation [1]. In fact, the available guidelines (SEPAR, BTS) suggest treating exacerbation with antibiotic therapy for 14 days [9, 10, 16].

15.6 Treatment of Exacerbations

As most exacerbations are considered to be the result of bacterial infections, current guidelines recommend antibiotic treatment [9, 10, 16]. As the microbiological etiology of exacerbation is quite variable, a sputum culture is suggested before

administering antibiotics in order to adjust treatment to microbiological results [9, 10, 16]. However, in the presence of previous chronic airway infections, the empiric antibiotic coverage should cover the microorganism formerly isolated [9, 10, 16]. In fact, some preliminary findings from a multicenter study show that the rate of concordance between the microbiology of chronic bronchial infection and exacerbation is about 80%, particularly in the case of chronic *P. aeruginosa*; in contrast, in the case of pneumonia, the microbiological etiology of exacerbation is often different from stable conditions and a complete microbiological investigation is recommended [66].

The choice of the antibiotic drug therefore depends on various factors, such as previous airway infection, allergies, intolerances and preferences, comorbidities (renal or hepatic failure), and concomitant medication, as well as on microbiological data when available. Only systemic antibiotics are currently recommended for the treatment of exacerbations, due to potential side effects or limited tolerability of inhaled antibiotics in these conditions (bronchospasm, wheezing, coughing) of the administration route (oral or intravenous) variable, depending on the severity of the exacerbation, drug availability, and pharmacokinetics and patient characteristics.

In case of *H. influenzae*, amoxicillin-clavulanic acid or doxycycline or a fluoroquinolone (levofloxacin or ciprofloxacin) are usually recommended (Table 15.2).

In case of *P. aeruginosa*, unfortunately the only active oral antibiotic is ciprofloxacin, which is generally used at the dosage of 750 mg BID. Alternatively, intravenous ceftazidime, carbapenem, piperacillin-tazobactam, or cefepime should be considered, according to antibiogram data. Despite the absence of scientific evidence regarding the use of combined antibiotic therapy in bronchiectasis, it is possible to consider it in case of severe exacerbations or mucoid or multidrug-resistant strains of *P. aeruginosa*. In particular, a combination therapy with tobramycin, colistin, gentamycin, or amikacin should be contemplated.

Unfortunately, an empiric antibiotic coverage is frequently needed due to the unavailability of a previous microbiological culture. In these cases, ciprofloxacin is usually recommended in order to cover the risk of *P. aeruginosa*, although in a recently diagnosed bronchiectasis patient with few or no previous exacerbations, amoxicillin-clavulanic can also be considered; it is highly recommended to perform a sputum culture before antibiotic administration in order to eventually adjust antibiotic therapy once microbiology results become available [9, 10] (Table 15.4).

Based on clinical practice, experts' opinions, and certain scientific evidence, 14 days of antibiotic therapy are usually recommended [9, 10, 16, 28, 77]. However, in cases of mild exacerbations with a prompt resolution of symptoms (fewer than 5 days) and potential viral infection, a shortened antibiotic course could be considered; however, clinical follow-up could be useful to ensure complete recovery. Similarly, in case of late or partial treatment response, a longer antibiotic therapy could be considered, although,if a treatment failure is suspected (clinical worsening despite antibiotic therapy or insufficient improvement at the end of the antibiotic cycle), a new microbiological investigation should be performed, and other non-infectious causes of clinical deterioration (such as pulmonary embolism or heart failure) should be investigated.

Table 15.4 Recommended antibiotic treatment according to the most common microbiology isolates in exacerbations of bronchiectasis

Microorganism	Chosen treatment	Alternative
Mild outpatient exacerbation		
Hemophilus influenzae	Amoxicillin/clavulanic acid 875/125 mg c/8 h oral or doxycycline 100 mg/12–24 h	Amoxicillin 1–2 g c/8 h oral ciprofloxacin 750 mg c/12 h oral
Pseudomonas aeruginosa	Ciprofloxacin 750 mg c/12 h oral	Levofloxacin 500 mg c/12 h oral
Staphylococcus aureus	Cloxacillin 500–1000 mg c/6 h oral	Amoxicillin/clavulanic acid 875/125 mg c/8 h oral + or levofloxacin 500 mg c/12 h oral
Moderate-to-severe exacerbation		
Haemophilus influenzae	Amoxicillin/clavulanic acid 1–2 g c/8 h IV	Ceftriaxone 2 g c/24 h IV
Pseudomonas aeruginosa	Ceftazidime 2 g c/8 h IV + amikacin 15–20 mg/kg c/24 h IV, or tobramycin 5–10 mg/kg c/24 h IV	Imipenem 1 g c/8 h IV, or meropenem 2 g c/8 h IV, or piperacillin/tazobactam 4 g c/8 h IV, or cefepime 2 g c/8 h IV, or aztreonam 2 g c/8 h IV, or ciprofloxacin 400 mg c/12 h IV + amikacin 15–20 mg/kg c/24 h IV
Staphylococcus aureus	Vancomycin 1 g c/12 h IV	Linezolid 600 mg c/12 h, or sodium colistimethate 1–2 mU c/12 h IV

In the case of high fever, C-reactive protein >5 mg/dl and unusual findings upon thoracic auscultation, a pneumonia should be ruled out through a chest X-ray or CT scan. In risk of *S. pneumoniae* should be covered, but also micro-organisms responsible for pre-existing chronic bronchial infections need to be considered [66, 78].

There are no specific recommendations regarding corticosteroids or inhaled bronchodilators for exacerbations of bronchiectasis, but their use usually follows general indications for these drugs [16]. With regard to inhaled hyperosmolar agents such as hypertonic saline or mannitol, there is scientific evidence to support their use during exacerbations. Moreover, the risk of side effects—such as bronchospasm—could be increased during exacerbations, due to increased airway inflammation.

In general, there is a widespread belief—among both doctors and patients—that airways' clearance techniques can facilitate and accelerate a patient's recovery from exacerbations. unfortunately there is no evidence that airways' clearance techniques can be useful during exacerbations to facilitate and accelerate patient recovery and further investigation is surely needed for the future.

15.7 Prevention of Exacerbations (Table 15.5)

15.7.1 Antibiotics

The long-term management of bronchiectasis is generally directed at preventing exacerbations; therefore, numerous recommendations appear in the Spanish and British guidelines [9, 10]. In particular, the use of chronic oral macrolides and

Table 15.5 Prevention of exacerbations

Intervention	Drug	Target population	Note
Oral antibiotics	Azithromycin, erythromycin	>3 exacerbations/year	Discard NTM infection, QTc prolongation
Inhaled antibiotics	Colistin, tobramycin, ciprofloxacin, gentamycin	>3 exacerbations/year	Use bronchodilators before antibiotic administration A supervised challenge test is recommended for first use
Hyperosmolar agents	Hypertonic saline (7%), mannitol	Abundant or difficult expectoration, poor quality of life, >3 exacerbations/year	Use bronchodilators prior to antibiotic administration A supervised challenge test is recommended on first use
Respiratory physiotherapy	Airway clearance techniques, pulmonary rehabilitation	Abundant or difficult expectoration; poor quality of life; dyspnea and or fatigue	Personalized intervention according to patient characteristics, needs, preferences, and availability of physiotherapist, devices, etc.
Vaccines	Anti-influenza, pneumococcal (PPSV23 or PCV13)	All patients with bronchiectasis	If PPSV23 has been administered in the past, wait 1 year before administering PCV13

inhaled antibiotics have been widely supported by experts worldwide. Since then, a number of interesting trials have provided increasing scientific evidence for these therapies. In particular, there have been three major randomized clinical trials (BLESS, EMBRACE, and BAT) that showed a clear reduction of exacerbations (time from the first exacerbation or frequency of exacerbations) with continued use of azithromycin (from 250 mg daily to 500 mg 3 times a week), or erythromycin (400 mg BID) [11–13].

Despite some methodological differences between these trials, the three of them can provide common evidence to recommend using these antibiotics in the cases of patients with three or more exacerbations in the previous year, despite optimization of therapeutic management. It is worth mentioning again that important adverse events have been reported so far; in particular, diarrhea and an increase in the proportion of macrolide-resistant microorganisms in the oropharyngeal mucosa (*Streptococci*) are quite common. Less frequent potential treatment-related adverse events, such as QTc prolongation, tinnitus/hearing loss, and selection of macrolide-resistant non-tuberculous mycobacteria (NTM) should be carefully considered when beginning long-term treatment with macrolides. In particular, 2–3 sputum cultures negative to NTM are recommended before beginning macrolides, since it is known that NTM infections caused by macrolide-resistant strains are usually more difficult to treat [79]. Conversely, other chronic regimens with oral antibiotics, such

as amoxicillin or tetracycline, have been reported to improve sputum purulence, but do not show such clear benefits in terms of exacerbations as frequently as macrolides [34, 80].

Most clinical experts in bronchiectasis feel that inhaled antibiotics are potentially the best option for reducing exacerbations in bronchiectasis due to the high local concentrations achieved in the airways, minimal systemic side effects, and limited occurrence of antibiotic resistance. Numerous antibiotics have been developed in the past few years for inhaled administration (e.g., dry powder, nebulized solutions); these include ciprofloxacin, aztreonam, colistin, and tobramycin. Unfortunately, the level of evidence supporting their use in clinical practice is still controversial due to the fact that, unexpectedly, some clinical trials failed to achieve primary outcomes. For instance, inhaled aztreonam, which had shown positive results for CF [81, 82], did not improve quality of life (primary outcome of the LQ-B questionnaire) significantly more than placebos [23]. Haworth et al (2014) could not prove that inhaled colistin could significantly prolong the time to the first exacerbation in the overall population (primary outcome). However, patients who stayed with the treatment during the trial, showed a median time to exacerbation of 168 (65) vs. 103 (37) days in the colistin and placebo groups, respectively ($P = 0.038$) [27].

Similar results were described in a study investigating the efficacy of nebulized liposomal ciprofloxacin in bronchiectasis patients with *P. aeruginosa* infection [14]. A 1-year single blind study of nebulized gentamicin showed a significant reduction in the frequency of exacerbations (0 [0–1] vs. 1.5 [1–2], $p < 0.0001$), compared to 0.9% saline-treated patients and a prolonged time to the first exacerbation (120 [87–161.5] d vs. 61.5 [20.7–122.7] d; $P = 0.02$) [83]. A 1-month phase II RCT investigating inhaled ciprofloxacin dry powder showed promising results in terms of microbiological response, [15] but results of the subsequent long-term phase III RCT are currently awaited [84]. Again, some relevant side effects have been described in association with the use of inhaled antibiotics, such as increased cough, bronchospasm, and breathlessness, while minimal or non-significant antimicrobial resistance are currently known. Very recently, the European Guidelines on bronchiectasis have suggested the use of inhaled antibiotics to prevent exacerbations of patients with chronic *P. aeruginosa* infection and the use of macrolides to prevent exacerbations of patients with any other chronic airways infection, although an individualized approach is always to be considered [16].

15.8 Mucolytic and Hyperosmolar Agents

Despite the fact that hypertonic saline has been proved to improve airways' clearance, quality of life, and FEV_1 in bronchiectasis when combined with respiratory physiotherapy [19, 85], there is still no evidence that its chronic use can prevent exacerbations. Considering these promising results and the low cost of this intervention, further investigation is surely an urgent need.

Other, more expensive hyperosmolar agents such as mannitol, failed to show a significant reduction in the annual frequency of exacerbation (primary outcome, rate ratio 0.92, $p = 0.31$). However, compared with low-dose mannitol control, mannitol prolonged time to the first exacerbation (HR 0.78, $p = 0.022$) and quality of life (−2.4 units, $p = 0.046$) (two secondary outcomes). Luckily, similar side effects were reported for both arms [18]. Otherwise, deoxyribonuclease (RhDNase) is currently contraindicated in bronchiectasis due to the fact that the only RCT showed an increased rate of exacerbation in association with this mucolytic agent, which is frequently used in CF [86].

15.9 Physiotherapy

Although respiratory physiotherapy is currently not recommended during exacerbations, its use in stable clinical conditions is considered a pillar in the long-term management of bronchiectasis. Ideally, excellent physiotherapy (including airway clearance techniques and/or pulmonary rehabilitation) is able to reduce mucus retention, limiting the accumulation of micro-organisms, inflammatory cells, and molecules. Therefore, physiotherapy should be able to disrupt the Cole vicious cycle that perpetuates lung damage in bronchiectasis.

Unfortunately, the scientific evidence regarding airway clearance techniques is extremely heterogeneous due to various methods of intervention and outcome measures. This heterogeneity makes it almost impossible to suggest a standardized protocol for airway clearance. Nonetheless, there are numerous studies that indicate the advantages of regular physiotherapy on sputum volume [87–89] and the impact of coughing on quality of life.

The airway clearance techniques are especially indicated in those patients with copious phlegm and/or difficult expectoration, but each intervention should be personalized, based on patients' characteristics and preferences, as well as the availability of physiotherapists and/or devices. Herrero-Cortina et al. compared autogenic drainage (a technique performed autonomously by patients), ELTGOL (requiring the intervention of a physiotherapist), and UNIKO, a temporary positive-expiratory-pressure (T-PEP) device, in a population of stable bronchiectasis patients. They could demonstrate that the three interventions achieved similar results by enhancing mucus clearance during treatment sessions and reducing expectoration for the rest of the day [90].

More evidence is available regarding the efficacy of pulmonary rehabilitation in improving exercise capacity and a trend towards better quality of life [22, 91–94].

Lee et al. performed a randomized controlled trial aimed at investigating the effects of exercise training and airway clearance techniques on exercise capacity, quality of life.

(HRQOL), and the incidence of acute exacerbations in bronchiectasis [22]. This is the only study found in the literature that shows that physiotherapy was able not

only to reduce dyspnea and increase exercise capacity, but also to reduce the incidence of exacerbations at 1 year.

As in COPD and CF, the regular performance of physical activity or pulmonary physiotherapy has to be recommended to all patients with bronchiectasis in order to reduce the overall burden of the disease in terms of respiratory symptoms (dyspnea, fatigue, cough, and expectoration) and to reduce frequency and severity of exacerbations. It is likely that all physiotherapeutic interventions will be useful in bronchiectasis if optimized and personalized to specific patients and health conditions. The recent European guidelines recommend the use of hypertonic saline or mannitol in bronchiectasis patients with chronic productive cough or difficulty to expectorate sputum and rehabilitation in case of impaired exercise capacity [16].

15.10 Vaccines

Unfortunately, there are no data regarding the efficacy of influenza and pneumococcal vaccines in the specific population of bronchiectasis. Nevertheless, the incidence of bronchiectasis increases exponentially in the elderly, and it is generally recommended to use vaccines both for influenza virus and pneumococcal infection in people >65 years old, particularly in cases of chronic respiratory diseases [95–97].

Moreover, it is well known that bronchiectasis patients suffer more pneumonias than the general population [78]. Since the first cause of community-acquired pneumonia in bronchiectasis is *S. pneumoniae*, it is wise to recommend pneumococcal vaccination to these patients in order to reduce respiratory morbidity [78]. While the 23-valent polysaccharide vaccine is widely and historically used in bronchiectasis to investigate the immune response (antibody production), the 13-valent conjugate vaccine was introduced only in the last few years, due to the recognized superiority in terms of reduced risk of pneumococcal pneumonia and of prolonged duration of protection (T-cell-mediated immunological memory) [98, 99].

Nevertheless, more tailored research is needed in the future to better develop strategies to prevent infections in this subset of the population with bronchiectasis.

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Long-Term Inhaled Antibiotic Treatment in Bronchiectasis

16

Michal Shteinberg, Chris Johnson, and Charles Haworth

16.1 Introduction

The vicious cycle hypothesis of bronchiectasis formation and propagation [1] defines a major role for airway bacterial infection. Bacterial infection leads to inflammation, airway damage and remodelling, with mucus accumulation which in turn leads to further bacterial growth in retained airway secretions. Experimental evidence correlating inflammation to bacterial colonisation supports this model. Markers of inflammation were found to be elevated in bronchial lavage fluids of patients with bronchiectasis compared to controls. These markers correlated with bacterial colony-forming unit (CFU) count [2, 3] and were higher in patients infected with *P. aeruginosa* compared to colonisation with other bacteria [3]. In a study investigating sputum bacteria and inflammatory markers in 385 patients with bronchiectasis, a correlation was found between airway bacterial density and inflammatory mediators, including IL-8, TNFα and IL-1β in sputum, as well as markers of systemic inflammation in serum- ICAM-1 and E-selectin. Both bacterial density and inflammatory mediator levels decreased after systemic or inhaled antibiotic treatment [4].

Several bacterial species are frequently found in bronchiectasis: among the most common are *P. aeruginosa*, *H. influenzae, S. aureus,* streptococci and non-tuberculous mycobacteria (NTM) [5–8]. Infection with *P. aeruginosa* is associated with adverse outcomes in bronchiectasis as well as in cystic fibrosis (CF): an increase in the frequency of exacerbations and hospitalisations, accelerated deterioration in lung function, decreased quality of life as well as increased mortality [7, 9–15]. Colonisation of the bronchiectatic airways with *H. influenzae* was also found

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to be associated with elevated inflammatory markers [3, 16], and colonisation with bacteria other than *Pseudomonas* (which in a large part represent *Haemophilus* colonisation) is associated with increased severity, although less than that found with *Pseudomonas* colonisation [10, 14]. Of special importance is infection with methicillin-resistant *S. aureus* (MRSA) and other enteric gram-negative bacteria. Infection with these organisms has been found to be associated with elevated mortality, exacerbations and hospitalisation as well as a reduced quality of life to an extent comparable to that of colonisation with *Pseudomonas* [10].

The adverse consequences of chronic infection are the basis for using long-term antibiotics in the treatment of stable bronchiectasis. Treatment goals that may be achieved with long-term antibiotics are eradication of bacteria from the airways to prevent bacterial colonisation, prevention of exacerbations and mortality in patients chronically colonised with bacteria, slowed deterioration of lung function and relief of symptoms—most importantly, cough and production of sputum [17, 18]. Some of these goals have been shown to be achievable with inhaled antibiotics.

16.2 Administration of Antibiotics by Inhalation

Administration of antibiotics by inhalation has the advantage of delivering high antibiotic concentrations directly to the site of the infection, while minimising systemic exposure and toxicity. Aminoglycosides, which are highly effective against *P. aeruginosa*, have limited penetrance to the lung when administered intravenously [19, 20]. Conversely, pharmacokinetic studies in CF patients exploring lung levels of tobramycin showed that administration of 300 mg tobramycin solution for inhalation (TSI) yields a sputum concentration 12-fold higher, with serum concentrations 7.5-fold lower, than when tobramycin is given intravenously [21–24].

Ideally, an inhaled antibiotic should be delivered to all infected areas of the lung. However, several factors may limit drug availability to the infected airways. An important determinant of particle deposition is the mean mass aerodynamic diameter (MMAD) of the drug. It has been demonstrated that inhalation of large particles results in oropharyngeal deposition, while the optimal particle size for deposition in the small airways is between 1 and 6 μm (Fig. 16.1) [25]. MMAD is determined by the combination of the drug and the nebuliser used and may not be the same for different drug-nebuliser combinations. Second, mucus plugging, resulting in narrowing of bronchi and turbulent air flow, may interfere with airflow and drug delivery to the site of inflammation [26]. Mucus in the inflamed airway may also interfere with antibiotic efficacy: aminoglycoside antimicrobial action was found to be inhibited by mucin, divalent cations and DNA that are components of airway secretions [22, 27].

Third, factors such as pH and the presence of preservatives may affect tolerance to inhaled antibiotics. Historically, intravenous preparations of antibiotics were given by nebulisation [28, 29]. The concern for safety and issues with tolerability of inhalation of preparations designed for intravenous use [30] led to the development of preparations for inhalations free from added preservatives [31], which has become widespread in the care of CF patients chronically colonised with *P. aeruginosa* [32, 33].

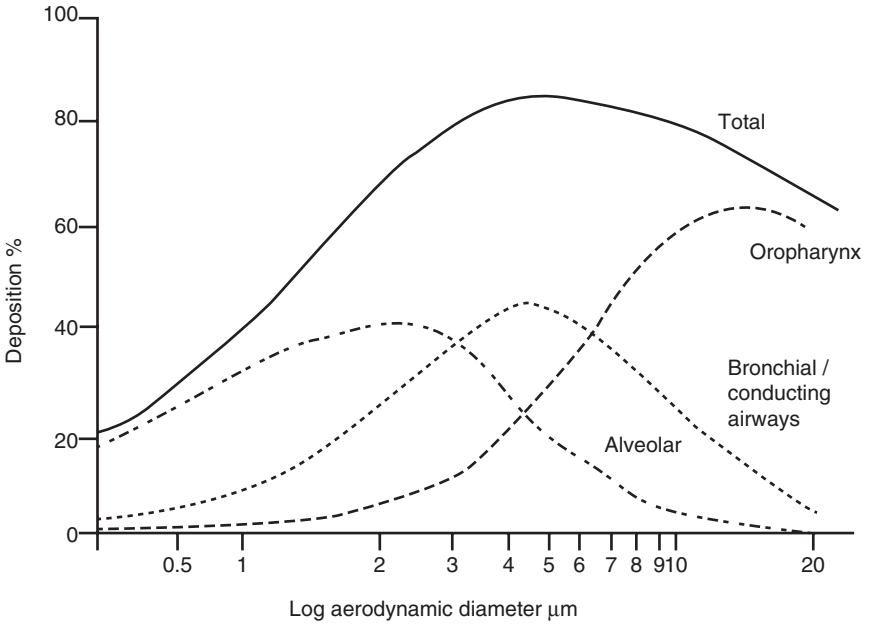

Fig. 16.1 The relationship between aerodynamic diameter and lung deposition. *This material has not been reviewed by the European Respiratory Society prior to release; therefore the European Respiratory Society may not be responsible for any errors, omissions or inaccuracies or for any consequences arising therefrom, in the content.* Reproduced with permission of the European Respiratory Society ©: Eur Respir J 2011; 37(6):1308–1417 [25]

16.3 Lessons Learned from CF

Inhaled antibiotic administration is well established in the care of CF patients. There is evidence that early treatment with inhaled antibiotics is effective in the eradication of *P. aeruginosa* infection when started early after first detection. Administration of TSI administered twice daily for 28 or 56 days was found to eradicate *P. aeruginosa* in the majority of subjects, with 70% being free from *P. aeruginosa* infection within a year [34]. In the EPIC trial, TSI was demonstrated to effectively eradicate early *P. aeruginosa* infection when used with or without ciprofloxacin [35]. Similar results have also been achieved with inhaled aztreonam lysine (Cayston®) in children with CF with a new isolation of *P. aeruginosa* [36]. For CF patients with established, chronic Infection with *P. aeruginosa*, chronic administration of inhaled antibiotics has the benefits of reducing pulmonary exacerbations and improving lung function as well as symptoms [37–41].

An important consideration in choosing an antibiotic for long-term inhalation is that inhaled antibiotics may be clinically effective even in cases when the antibiogram done on a sputum sample may indicate resistance of the bacteria to the antibiotic used [42]. This finding may be explained by two ways: (1) The antibiogram is

a method developed for blood samples and may not reflect the conditions in sputum whose contents may affect bacterial growth. (2) Inhaled antibiotics reach concentrations in airways that are severalfold higher than the MIC. In studies of prolonged use of inhaled antibiotics in CF, an increase in bacterial resistance was observed, although efficacy was not reduced [23, 31, 38].

16.4 Why Bronchiectasis Is Not Cystic Fibrosis

Many of the treatments employed in the care of bronchiectasis are extrapolated from CF patient care. The use of inhaled antibiotics for chronic infected patients with bronchiectasis has the potential to be as beneficial as in CF. However, several differences between CF and bronchiectasis may determine difference in outcomes. First, bronchiectasis patients are older (mean age of 60+ years) with more prevalent comorbidities than CF patients, and these factors may impose difficulties in handling nebulized medications and reduce tolerability to inhaled agents [43–46]. Second, concomitant chronic medications may differ between patients with CF and patients with bronchiectasis: specifically, the use of rhDNAse, which is widespread among patients with CF but not among patients with bronchiectasis, may change the properties of mucus and increase the effectiveness of the inhaled antibiotic. Finally, in many health settings, the availability of resources—e.g., modern nebulisers, access to physiotherapists and chest clearance—is different between patients with CF and patients with bronchiectasis. These factors underscore the importance of conducting clinical trials and 'real-life' studies designed for patients with bronchiectasis to test the efficacy of inhaled antibiotics.

16.5 Studies of Inhaled Antimicrobials in Bronchiectasis

Inhaled antibiotic studies in bronchiectasis have almost exclusively evaluated antipseudomonal agents including aminoglycosides, colistin, beta lactams and quinolones. However, the earliest studies investigated the efficacy of nebulised amoxicillin, predominantly in patients with *H. influenzae* [47–49]. While the results were largely positive, showing reductions in inflammatory biomarkers, sputum volume and purulence, in clinical practice long-term oral antibiotics such as amoxicillin or doxycycline are used most commonly in patients with *H. influenzae* as they are easier and cheaper to administer.

16.5.1 Tobramycin

There have been four moderately sized studies evaluating nebulised tobramycin as chronic suppressive therapy in patients with bronchiectasis and one study evaluating the use of nebulised tobramycin in acute exacerbations of bronchiectasis [43–46].

In a study involving patients with bronchiectasis infected with *P. aeruginosa*, participants were randomised to receive TSI ($n = 37$) or placebo ($n = 37$) twice daily for 4 weeks [43]. At week 4, the TSI group had a mean decrease in *P. aeruginosa* density of 4.5 $\log_{10}$ colony-forming units per gram (CFU/g) of sputum compared with no change in the placebo group ($p < 0.01$). Logistic regression analysis identified that decreases in CFU/g of sputum were significant predictors of improved well-being. Two weeks after treatment was completed, *P. aeruginosa* was eradicated in 35% of the TSI group but was detected in all placebo patients. Sixty-two percent of TSI patients showed improvement in their medical condition versus 38% of placebo patients (odds ratio 2.7, 95% confidence interval 1.1–6.9), but there was no significant change in lung function between the groups. Tobramycin-resistant *P. aeruginosa* strains developed in 4/36 (11%) of TSI-treated patients and 1/32 (3%) of placebo patients. Three of the four patients in the TSI group who developed resistant *P. aeruginosa* strains showed no microbiological response, and all four failed to improve clinically. Adverse events such as cough, breathlessness, wheezing and chest pain were more common in TSI-treated patients compared with placebo patients, but did not appear to limit therapy.

A second trial evaluating TSI involved 41 patients with bronchiectasis and *P. aeruginosa*. The study was open label, and patients took three treatment cycles (14 days of TSI and 14 days off) [46]. During the 12-week treatment period, there were significant improvements in pulmonary symptoms and quality of life. However, tobramycin-resistant strains of *P. aeruginosa* developed in two subjects, and ten patients dropped out due to adverse events, the most common being cough, wheeze and breathlessness.

An alternative formulation of nebulised tobramycin was evaluated in a double-blind placebo-controlled crossover trial [44]. Thirty patients nebulised tobramycin 300 mg or placebo twice daily for 6 months, with a 1-month washout period between treatments. Only 20 patients completed the protocol, as three withdrew due to bronchospasm, five died from respiratory failure and two others dropped out. While the number of admissions and inpatient days reduced during treatment with nebulised tobramycin and there was a decrease in *P. aeruginosa* density, there was no significant difference in the number of exacerbations, antibiotic use, lung function or quality of life between the tobramycin and placebo treatment periods.

In a 12-month open-label study, patients with bronchiectasis were randomised to receive nebulised ceftazidime 1 g bd + tobramycin 100 mg bd or symptomatic treatment [45]. While there were significantly less admissions and inpatient days in the nebulised antibiotic group, there was no difference in the use of oral antibiotics between the two treatment groups. There was also no difference in the emergence of antibiotic-resistant bacteria between the treatment groups.

In summary, nebulised tobramycin used for chronic bacterial suppression has shown impressive microbiological and clinical outcomes, but poor tolerability has limited its development in patients with bronchiectasis. Furthermore, TSI showed promise as an adjunct to ciprofloxacin in a trial of exacerbation treatment, but its use for this indication was also associated with a high incidence of adverse events [50].

16.5.2 Gentamicin

There has been one proof of concept study and a single centre evaluation of nebulised gentamicin in patients with bronchiectasis. In a randomised controlled trial of nebulised gentamicin 40 mg (n = 16) vs 0.45% saline (n = 15) administered twice daily for 3 days [51], nebulised gentamicin resulted in significant improvements in sputum volume, sputum inflammatory biomarkers, peak expiratory flow rate and 6-min walk distances. In a longer-term study, 65 patients with bronchiectasis were randomised to receive nebulised gentamicin 80 mg or 0.9% saline twice daily for 12 months [52]. The majority of patients were infected with *H. influenzae* or *P. aeruginosa*. Nebulised gentamicin was associated with significant reductions in bacterial density with a 31% eradication rate in patients infected with *P. aeruginosa* and a 93% eradication rate in patients infected with other pathogens. There were also significant improvements in sputum purulence, greater exercise capacity, exacerbation frequency, time to first exacerbation and quality of life with nebulised gentamicin. There were no major safety concerns raised by the prolonged administration of inhaled aminoglycosides in this study, and in particular, there was no development of gentamicin-resistant *P. aeruginosa*.

16.5.3 Colistin

Small retrospective studies have suggested that nebulised colistin may be beneficial in bronchiectasis patients with *P. aeruginosa* infection in terms of exacerbation frequency, admission rates, sputum volume and lung function [53, 54]. More recently, a phase III trial of nebulised colistin (Promixin) delivered via an adaptive aerosol delivery device capable of monitoring adherence (I-Neb, Philips Respironics, Chichester, UK) was reported [55]. Patients with bronchiectasis and *P. aeruginosa* were enrolled within 3 weeks of completing a course of anti-pseudomonal antibiotics. Participants were randomised to receive active treatment (nebulised Promixin 1MU in 1 mL 0.45% saline) or placebo (1 mL 0.45% saline) twice daily until first exacerbation for a maximum of 6 months. The primary endpoint was time to exacerbation with secondary endpoints including time to exacerbation based on adherence data downloaded from I-Neb, bacterial density and health-related quality of life score. The time to first exacerbation was not significantly different between the Promixin and placebo groups (165 vs 111 days, p = 0.11, respectively). However, in adherent patients (those who took 80% or more of doses), time to first exacerbation was 168 days in the Promixin-treated patients compared to 103 days in those receiving placebo (Fig. 16.2), a finding that is statistically (p = 0.028) and clinically significant. In the whole group analysis, the use of Promixin was also associated with a significant reduction in *P. aeruginosa* density and an improvement in quality of life compared to placebo. Finally, there were no concerns regarding tolerability, the development of colistin resistance or treatment-emergent organisms.

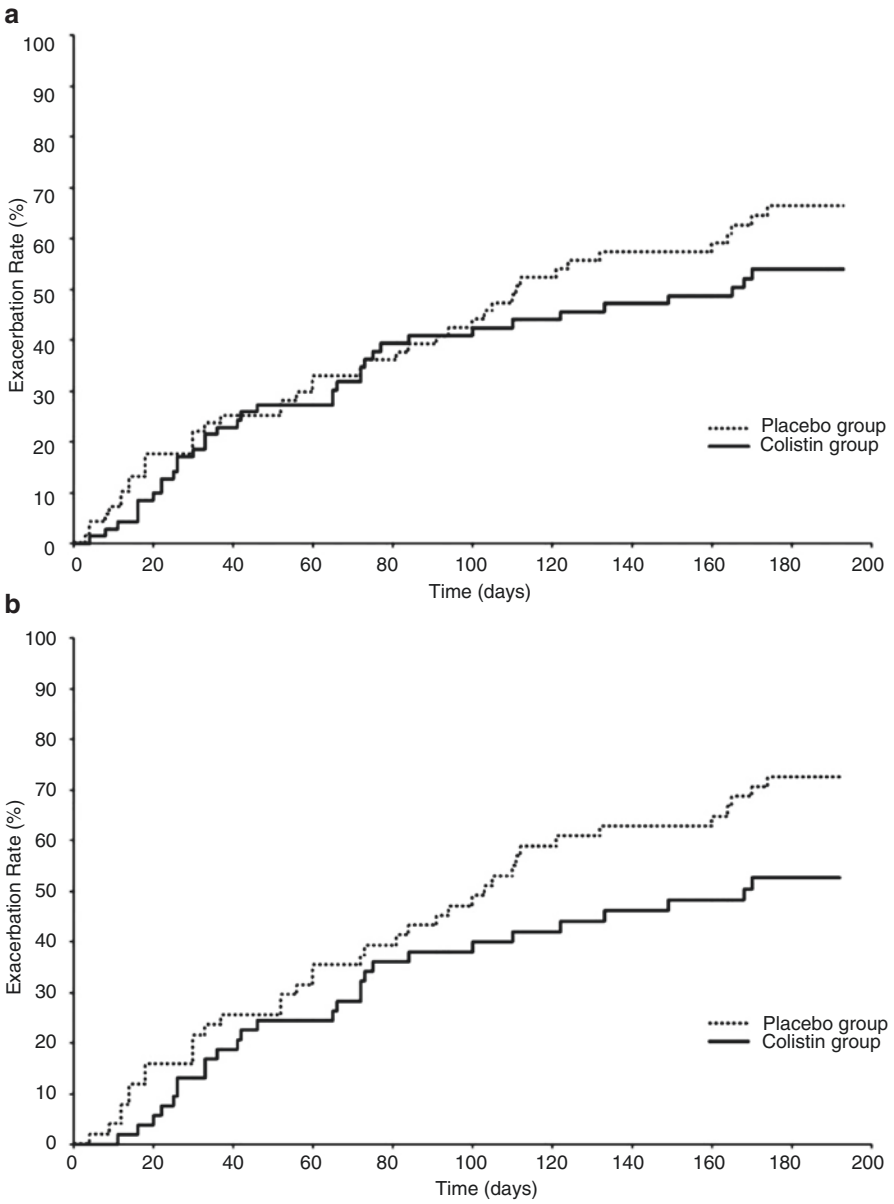

Fig. 16.2 Kaplan-Meier plot of estimate of time to first exacerbation with nebulised colistin and placebo delivered through the I-neb within (**a**) the whole intention-to-treat population and (**b**) adherence quartiles 2–4 of the intention-to-treat population. Reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society. Haworth CS, Foweraker JE, Wilkinson P, Bilton D. Inhaled colistin in patients with bronchiectasis. Am J Respir Crit Care Med. 2014;189:975–982. The *American Journal of Respiratory and Criticial Care Medicine* is an official journal of the American Thoracic Society [55]

16.5.4 Aztreonam

Aztreonam is a monobactam active against gram-negative organisms including *P. aeruginosa* and *H. influenzae.* The safety and efficacy of aztreonam lysine for inhalation (AZLI) was examined in two large randomised double-blind, placebo-controlled trials in bronchiectasis, AIR-BX1 and AIR-BX2 [56]. Five hundred and forty patients were randomised to receive nebulised AZLI 75 mg or placebo thrice daily for two treatment cycles (month on, month off). The primary endpoint was change in Quality of Life-Bronchiectasis (QOL-B) Respiratory Symptoms Score (RSS) between baseline and 4 weeks. Secondary endpoints included change in QOL-B RSS between baseline and week 12 and time to first exacerbation. The difference between AZLI and placebo for adjusted mean change from baseline QOL-B-RSS was not significant at 4 weeks (0.8 [95% CI-3.1–4.7], $p = 0.68$) in AIRBX1, but was significant (4.6 [1.1–8.2], $p = 0.011$) in AIR-BX2. However, the 4.6-point difference in QOL-B-RSS after 4 weeks in AIR-BX2 was not deemed clinically significant. In both studies, treatment-related adverse events were more common in the AZLI group than in the placebo group, as were discontinuations from adverse events. The most commonly reported treatment-emergent adverse events were dyspnoea, cough and increased sputum production. Each was more common in AZLI-treated than placebo-treated patients. The quantitative microbiology showed a significant reduction in bacterial density during treatment with AZLI. However, there was evidence of increasing bacterial resistance in those receiving AZLI and a less marked reduction in bacterial density in the second treatment cycle.

There are a number of possible explanations for this negative result: infrequent exacerbators were enrolled with only approximately 20% of participants having had three or more exacerbations in the previous year; patients infected with organisms not sensitive to aztreonam were included; only 80% of patients were infected with *P. aeruginosa,* the organism against which AZLI has most proven benefit (in people with CF); the intervention was limited to just two treatment cycles; dose-finding studies in people with bronchiectasis were not carried out, which may explain the higher than expected adverse events with AZLI in this patient population; and the primary endpoint was a recently developed quality of life score rather than an exacerbation endpoint.

16.5.5 Ciprofloxacin

Ciprofloxacin is commonly used in the treatment of acute exacerbations of bronchiectasis, but recently it has been reformulated into a liposomal preparation for nebulisation and into a dry powder for inhalation.

Dual-release ciprofloxacin for inhalation (DRCFI) was evaluated in a phase II randomised placebo-controlled trial involving 42 patients with bronchiectasis and ciprofloxacin-sensitive *P. aeruginosa* infection [57]. Participants received DRCFI or placebo for 3-month on/3-month off cycles. The primary outcome measure was change in *P. aeruginosa* density, and secondary outcomes included time to first

exacerbation and safety parameters. Study drug was discontinued if a participant had an exacerbation. DRCFI resulted in a mean (SD) 4.2 (3.7) $\log_{10}$ CFU/g reduction in *P. aeruginosa* density at day 28 compared to −0.08 (3.8) $\log_{10}$ CFU/g reduction with placebo, $p = 0.002$. DRCFI treatment delayed time to first pulmonary exacerbation (median 134 vs 58 days, $p = 0.057$ in the modified intention to treat analysis; $p = 0.046$ in the per protocol analysis) and was well tolerated with a similar incidence of systemic adverse events to the placebo group.

In a phase II study of ciprofloxacin dry powder for inhalation (DPI), 124 patients with bronchiectasis and predefined respiratory pathogens (predominantly *H. influenzae* and *P. aeruginosa*) were randomised to ciprofloxacin DPI 32.5 mg or placebo twice daily for 1 month [58]. Treatment with ciprofloxacin DPI was associated with a significant reduction in sputum bacterial load compared to placebo (−3.6 log10 CFU/g versus −0.27 CFU/g, $p < 0.001$) and was well tolerated.

In a recent meta-analysis investigating all trials of inhaled antibiotics in patients with bronchiectasis, Yang et al. [59] have found the following benefits: (1) reduction of bacterial density in sputum by 2.85 (95% CI, 1.6, 4.09, $p < 0.00001$) while achieving in some cases eradication of *Pseudomonas* from sputum (OR 6.6, 95% CI 2.93, 14.86, $p < 0.00001$); (2) reduced risk of exacerbations (OR 0.46, 95%CI, 0.21–1, $p = 0.05$); (3) no evidence of emergence of resistant bacteria following treatment with inhaled antibiotics; and (4) adverse events more common with inhaled antibiotics were wheeze, bronchospasm and abnormal taste (Table 16.1).

PA Pseudomonas aeruginosa, *SGRQ* St. George Respiratory Questionnaire, *TIS* tobramycin inhalation solution

16.6 Current Studies

DRCFI and ciprofloxacin DPI have been further evaluated in pivotal phase III multicentre randomised controlled studies that are due to report shortly. The RESPIRE trial included patients with colonisation with bacteria other than *P. aeruginosa*, and its results may be of importance to these patients with non-pseudomonal infection and exacerbations. A phase II dose-/regimen-finding study of tobramycin inhalation powder is about to start enrolment. A summary of ongoing trials is shown in Table 16.2. To date, there are no inhaled antibiotic preparations licenced specifically for patients with bronchiectasis.

16.7 The Complexity of Performing Inhaled Antibiotic Trials in Patients with Bronchiectasis

Through performing the clinical trials outlined above, pharma companies and the clinical community have identified a number of factors that could affect the outcome of clinical trials in patients with bronchiectasis: (1) The term bronchiectasis describes lung damage that is caused by a variety of disease processes which might respond differently to inhaled antibiotic therapy. While some investigators have

Table 16.1 Published trials of long-term inhaled antibiotics in bronchiectasis

Author, year [reference]	Total number of patients	Main inclusion criteria and bacterial colonisation	Inhaled antibiotics (comparator)	Duration of treatment	Results	Comments
Stockley, 1985 [48]	6	Purulent secretions after oral amoxicillin, diverse bacteria	Amoxicillin	4 months	Improvement in sputum purulence, volume and expiratory flow rate	
Barker, 2000 [43]	74	Chronic infection with PA	Tobramycin solution for inhalation (TSI) (placebo)	4 weeks	Reduction in bacterial density, eradication of bacteria	More TSI patients experienced cough and wheeze
Drobnic, 2005 [44]	30	Chronic infection with PA	Tobramycin solution for inhalation (TSI) (placebo crossover)	6 months	Reduction in admissions and admission days, decrease in PA sputum density	No reduction in overall no. of exacerbations
Scheinberg, 2005 [46]	41	Diffuse bronchiectasis in ≥2 lobes, chronic infection with PA	Tobramycin solution for inhalation (TSI)	12 weeks (2 weeks on/off cycles)	Improvement in symptom score, SGRQ, disappearance of PA in 22%	10 withdrew due to adverse events
Murray, 2011 [52]	65	Chronic bacterial infection, ≥2 exacerbations in preceding year	Gentamycin (placebo)	12 months	Reduced sputum bacterial density, less purulence, greater exercise capacity, less exacerbations	31% eradication of PA, 93% eradication of other pathogens
Haworth, 2014 [55]	144	Chronic PA infection, ≥2 exacerbations in preceding year, within 21 days of systemic antibiotic.	Colistin (placebo)	6 months	Longer time to exacerbation in adherent patients, reduced PA density, improved SGRQ score	Well tolerated

Author, year [reference]	Total number of patients	Main inclusion criteria and bacterial colonisation	Inhaled antibiotics (comparator)	Duration of treatment	Results	Comments
Barker, 2014 [56]	348	Infection with gram-negative bacteria	Aztreonam (placebo)	12 weeks (on/off)	QOL-significant benefit in one of two studies, not clinically significant	
Serisier, 2013 [57]	42	Chronic ciprofloxacin-sensitive PA infection, ≥2 exacerbations in preceding year	Once daily, dual release- liposomal and water soluble ciprofloxacin (placebo)	12 weeks, on/off cycles	Reduction in PA density, delayed time to pulmonary exacerbation	Well tolerated
Wilson, 2013 [58]	124	Chronic bacterial infection (diverse) ≥2 exacerbations in preceding year	Twice daily ciprofloxacin dry powder via inhaler (placebo)	28 days	Reduction in bacterial load, 35% eradication	Well tolerated

Table 16.2 Ongoing trials of inhaled antibiotics in bronchiectasis

Study	Phase	NIH identifier	Drug	Status
ORBIT-3 and ORBIT-4	III	NCT02104245	Cipro	Press release
RESPIRE 1	III	NCT01764841	Dry powder Ciprofloxacin	In preparation
RESPIRE 2	III	NCT02106832	Dry powder Ciprofloxacin	Waiting for results
Groningen	I, II	NCT02035488	Dry powder Tobramycin	Completed
Shandong	IV	NCT01677403	Tobramycin	U/K
ARIKACE	I, II	NCT00775138	LAI	Completed
BATTLE	II, III	NCT02657473	TSI	Enrolling
iBEST	II	NCT02712983	TIP	Ready to enrol
Z7224L01	III	2015-002743-33	Promixin	Not yet enrolling

tried to create a more uniform trial population by only including 'postinfective' or 'idiopathic bronchiectasis', accurately ascribing causation is dependent on the sophistication of the diagnostic workup and is often subjective. As a consequence, the true aetiology of bronchiectasis clinical trial participants is likely to be heterogeneous. (2) Until recently [10, 14], there were no validated scoring systems to measure disease severity in people with bronchiectasis, which could result in an imbalance between treatment groups. (3) Individuals with bronchiectasis often have polymicrobial infection [7], and trial inclusion/exclusion criteria must be appropriate for the antibiotic under investigation. (4) The absence of standardised and validated outcome measures (e.g. for exacerbation) has hampered evaluation of treatment efficacy within and between trials. (5) Antibiotic studies risk being underpowered if anticipated changes in exacerbation frequency are derived from historical exacerbation data (as this is subject to recall bias and the threshold for starting exacerbation antibiotics in clinical practice is often lower than that required in a clinical trial). (6) Differences in treatment approach/clinical experience between trial sites can influence key outcomes such as exacerbation frequency.

16.8 Inhaled Antibiotic Use in Clinical Practice

Patients with bronchiectasis and *P. aeruginosa* chronic infection tend to have more severe lung disease, a faster rate of lung function decline, more admissions to hospital, a worse quality of life and greater mortality compared to patients with other microorganisms [10, 13, 14, 60–65]. Thus, nebulised antibiotics are often prescribed in this context with the expectation that exacerbation frequency/disease progression will be reduced, consistent with CF management principals.

For individuals with *P. aeruginosa*, the available evidence supports the use of nebulised colistin [55] or gentamicin [52], and other options may become available if the quinolone trials are positive. Nebulised aztreonam is not recommended due to the poor efficacy and high adverse event rate reported in the phase III trials [56]. In

individuals infected with other organisms (such *H. influenzae*, *S. pneumoniae*, *Klebsiella* species or coliforms) and a high exacerbation frequency/history of severe exacerbation despite optimal oral antibiotic prophylaxis, a trial of nebulised gentamicin or amoxicillin may be indicated. The frequency of exacerbation that merits the introduction of antibiotic prophylaxis is debatable, but current guidance suggests three or more exacerbations may be an appropriate threshold [66]. Further research is required to determine if cyclical or continuous inhaled antibiotic regimens (possibly involving combinations of preparations) are optimal in terms of reducing exacerbation frequency, treatment burden and antimicrobial resistance. Reassuringly, antimicrobial resistance did not develop in the longer-term inhaled antibiotic trials to date [52, 55, 57], in contrast to the studies of azithromycin/erythromycin [67, 68], which may reflect the class of antibiotics used or the high antibiotic concentrations achieved within the airway through the inhaled route. In a retrospective analysis of 91 patients with bronchiectasis treated in a single bronchiectasis centre, 31 were treated with long-term inhaled antibiotics. Patients chosen for treatment with inhaled antibiotics (mostly inhaled tobramycin) had more exacerbations and a higher severity score, and more of them were treated with airway clearance and macrolides than untreated patients. In the year following initiation of treatment with inhaled antibiotics, exacerbations were significantly reduced compared to the year before commencing treatment ($p = 0.003$) [69]. While this trial is retrospective, its importance is in reflecting the benefit in 'real life' that may be achieved with inhaled antibiotics.

Before considering instituting long-term inhaled antibiotic treatment, generic components of bronchiectasis management need to be optimised (e.g. airway clearance) and other modifiable causes of instability (such as poor adherence to treatment) addressed. Careful characterisation of sputum pathogens (bacteria, mycobacteria and fungi) before and after implementation of inhaled antibiotics is essential to direct antibiotic choices, to monitor resistance patterns and to identify treatment-emergent organisms. Consideration should be given to a course of targeted intravenous antibiotics prior to implementation, as well as a trial of long-term treatment with a macrolide, which has been shown to prevent exacerbations [67, 68, 70]. Drug toxicity monitoring is also required, most notably with inhaled aminoglycosides (serum creatinine, audiometry). Adherence to inhaled antibiotic therapy is a major factor determinant of treatment success (Fig. 16.2) [55], and it is unknown if faster nebulisers (such as the Philips I-neb or PARI eFlow rapid), dry powder inhalers or the use of electronic adherence monitoring is associated with enhanced adherence and better long-term outcomes.

Patients should receive a supervised test dose of the nebulised antibiotic with pre- and post-spirometry and further follow up lung function 1 month after commencing treatment to assess efficacy and tolerability. Each patient should be carefully counselled regarding the side effect profile of treatment and that these treatments are currently unlicenced for use in people with bronchiectasis. Finally, careful documentation of clinical response including exacerbation rate and symptoms is essential to prove efficacy on an individual level.

Conclusion

Inhaled antibiotics offer the potential to reduce exacerbation frequency and slow disease progression in patients with bronchiectasis, while avoiding much of the systemic toxicity associated with parenteral antibiotic administration. At present, inhaled antibiotics are most commonly prescribed to patients with bronchiectasis complicated by chronic *P. aeruginosa* infection, due to the poor outcomes associated with this organism. The available evidence suggests that nebulised colistin is the most appropriate first-line maintenance antibiotic for this indication. Other inhaled antibiotics (such as gentamicin) might also be beneficial in bronchiectasis patients colonised with non-*Pseudomonas* species in the context of a high exacerbation frequency/impaired quality of life despite oral maintenance antibiotic therapy and optimisation of other aspects of their care. While it has proven challenging to gain regulatory approval for new inhaled antibiotics in patients with bronchiectasis, the great unmet clinical need and market opportunities have been recognised by pharma, and those clinical trials in progress or being planned will hopefully result in new products being licenced in the foreseeable future.

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Long-Term Oral Antibiotic and Anti-inflammatory Treatment

17

Pieter Christian Goeminne and Menno Van der Eerden

Bronchiectasis is a disease which is characterized by airway bacterial colonization, airway inflammation, and the occurrence of recurrent exacerbations [1]. The vicious circle hypothesis of Cole typically shows that these events will ultimately result in progressive damage to the airways (Fig. 17.1), lung function decline, and an increased risk of mortality [2]. In a European study, a strong relationship was observed between the annual frequency of exacerbations and future mortality, hospital admissions, exacerbations, and quality of life [3].

Maintenance treatment for bronchiectasis is directed at preventing the occurrence of exacerbations and to reduce chronic symptoms, and as such improving quality of life. To achieve this, it is necessary to intervene in the different steps of the vicious circle. Since the cycle is driven by both inflammation and infection, ideally both processes should be downregulated. Both anti-inflammatory and antibacterial treatment or a combination of both would hypothetically be candidates to "break" the circle and as such slow down disease progression and prevent further exacerbations.

17.1 Macrolides

17.1.1 Introduction

Macrolides are antibiotics which are traditionally used for their antibacterial effects in acute respiratory infections, like community-acquired pneumonia (CAP) [4], but

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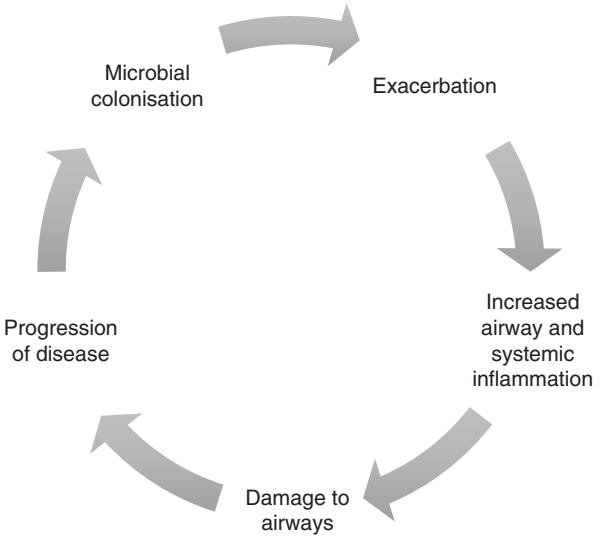

Fig. 17.1 Vicious circle hypothesis of bronchiectasis [2]. Reproduced with permission from the European Respiratory Society©. Eur J Respir Dis Suppl 1986;147:6–15

are more and more used because of their immune modulatory effects in chronic inflammatory pulmonary diseases, such as bronchiectasis [5]. The group of macrolides have in common that they possess a macrolide ring, which consists of 12 or more binding sites. Erythromycin and clarithromycin have a 14-membered ring, while the ring of azithromycin contains 15 members [6]. The antibacterial effect of macrolides is mainly bacteriostatic by binding to the 50S subunit of the bacterial ribosome, thereby inhibiting further bacterial protein synthesis. Infections caused by gram-positive microorganisms like *Streptococcus pneumoniae* and *Haemophilus influenzae* may be treated with macrolides, but also infections caused by atypical microorganisms like *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae* [7], because of their tendency to accumulate intracellularly. Accumulation inside neutrophils has been shown to cause high levels of erythromycin and azithromycin at the site of infection which is typically rich in neutrophils. Azithromycin is the macrolide with the best accumulation in leukocytes and with a longer half-life in (infectious) tissue as compared to erythromycin [8].

17.1.2 Macrolide Experience in Other Respiratory Diseases

More than two decades ago the beneficial effects of macrolides in diffuse panbronchiolitis resulted in its experimental use in other respiratory conditions. Bronchiectasis (both cystic fibrosis [CF] and non-CF) was the first disease to follow this path. Later on, macrolides were subsequently investigated in many other respiratory diseases. Here we bring a brief overview of the use of macrolides in other respiratory disease.

17.1.2.1 Diffuse Panbronchiolitis

First reports of diffuse panbronchiolitis showed a poor 5-year survival of 63% during the 1970s. One decade later, Kudoh et al. discovered that the prognosis of this disease in patients chronically treated with erythromycin improved dramatically [9]. This was later confirmed in several open-label trials with erythromycin and azithromycin [10–12]. Because of this dramatic effect and spectacular increase in survival, macrolides became standard treatment for diffuse panbronchiolitis. A recent Cochrane review highlights the absence of high-quality evidence to support the use of macrolides in the treatment of diffuse panbronchiolitis, but also states that macrolides should still be used soon after the diagnosis is made and should be continued for at least 6 months, according to current guidelines [13, 14].

17.1.2.2 Chronic Obstructive Pulmonary Disease (COPD)

COPD is a prevalent disease, and acute exacerbations have a serious negative effect on loss of lung function, mortality, healthcare cost, and quality of life. Any intervention that might reduce the number of exacerbations might therefore be very important in the course of this chronic disease. In patients with these frequent exacerbations, azithromycin 250 mg daily or 500 mg three times a week decreased the frequency of exacerbations and improved quality of life but also increased colonization with macrolide-resistant microorganisms [15, 16]. Similar trends were seen in stable COPD patients where a daily dose of 250 mg azithromycin reduced severe exacerbations and inflammatory markers [17].

17.1.2.3 Asthma

Several studies have tried to elucidate the effect of azithromycin on asthma exacerbations. As asthma is a heterogeneous disease, encompassing both eosinophilic and neutrophilic inflammatory phenotypes, it's speculated that macrolides might be beneficial in neutrophilic asthma. The AZISAST study by Brusselle et al. confirmed that a dosing scheme of azithromycin 250 mg three times a week showed no benefit in a general asthma population compared to placebo. However, a predefined subgroup analysis showed that patients with a non-eosinophilic asthma phenotype (defined as blood eosinophils equal or lower than 200/μl) had significantly less severe exacerbations when given azithromycin [18].

17.1.2.4 Cystic Fibrosis

CF is characterized by the development of bronchiectasis. For adults, azithromycin significantly diminished the rate of lung function decline, improved quality of life, reduced inflammation, and more importantly reduced the number of respiratory exacerbations [19]. A Cochrane meta-analysis confirmed these positive effects on lung function and exacerbations [20]. Macrolides are currently an essential part of the treatment of patients with CF.

17.1.2.5 Lung Transplantation and Bronchiolitis Obliterans Syndrome

In several end-stage lung diseases, lung transplantation is often the only therapeutic option left. However, mortality rates post-transplantation are still higher compared to other solid organ transplants. More specifically, chronic rejection is an important cause of death and is characterized by obliterative bronchiolitis. Recent trials have shown that chronic azithromycin treatment both improved FEV_1 in patients with obliterative bronchiolitis and also reduced the occurrence of obliterative bronchiolitis and increased FEV_1 when started post-transplantation [21, 22]. The presence of high numbers of airway neutrophils was found to show a positive correlation with a beneficial effect of macrolides.

17.1.3 Randomized, Placebo-Controlled Studies in Bronchiectasis

Three main randomized, double-blind, placebo-controlled studies, investigating the effect of azithromycin in bronchiectasis, have been performed (see Table 17.1). The first trial performed by Wong et al. included patients with at least one exacerbation in the year before trial inclusion [23]. Patients received azithromycin 500 mg three times a week or placebo for a period of 6 months. In this EMBRACE study, a significant reduction in exacerbations was observed. Another finding was that the beneficial effect of macrolide treatment persisted for 6 months after completion of treatment. Altenburg et al. also used azithromycin compared to placebo in their BAT study [5]. In contrast to the EMBRACE study, the BAT trial included patients with frequent exacerbations. Patients with at least three lower respiratory tract infections in the previous year were included. Another difference with the EMBRACE trial

Table 17.1 Randomized, double-blind, placebo-controlled trials with long-term macrolides in bronchiectasis

First author	Inclusion criteria	Intervention	Length of study	Number of exacerbations
Wong	– 18 years or older – ≥1 exacerbation requiring AB in preceding year	AZM 500 mg 3 times a week	6 months	Significantly reduced number of exacerbations (RR 0.38)
Serisier	– Age 20–85 years – ≥2 exacerbations requiring AB in preceding year	ERM 400 mg bid	48 weeks	Significantly reduced number of exacerbations (RR 0.57)
Altenburg	– Age ≥ 18 years – ≥3 LRTI requiring AB in preceding year – ≥1 sputum culture yielding ≥1 bacterial pathogen in preceding year	AZM 250 mg od	52 weeks	Significantly reduced number of exacerbations (RR 0.41)

was the dosage of azithromycin; in the BAT trial, patients received azithromycin 250 mg once daily. With this alternative dosing scheme, a significant reduction in exacerbations was observed, besides a significant improvement of lung function and quality of life parameters. In contrast to azithromycin, Serisier et al. used erythromycin in their BLESS trial [24]. The beneficial effects of this macrolide were reflected in a significant decrease in exacerbations, less sputum production, and increased eradication of sputum pathogens.

RCT randomized controlled trial, *AZM* azithromycin, *ERM* erythromycin, *od* once daily, *bid* twice daily, *HR* hazard ratio, *RR* rate ratio, *LRTI* lower respiratory tract infections, *IV* intravenous, *AB* antibiotic(s)

17.1.4 Working Mechanisms of Macrolides

Macrolides are protein synthesis inhibitors and work by inhibiting bacterial protein synthesis through reversible binding to the P site on the 50S subunit of the bacterial ribosome. They are mainly active against gram-positive organisms but have some limited gram-negative activity. Another important feature of macrolides is their increased retention in cells achieving high intracellular concentration in human cells. This causes them to be often effective against bacteria with in vitro resistance as they reach intracellular concentration way beyond the MIC.

Apart from this antibiotic activity, macrolides are thought to have multiple other mechanisms of action [25]. Macrolides are considered to alter the bacterial biofilm by inhibiting the polysaccharide synthesis [26]. They further suppress bacterial communication (quorum sensing), adherence to airway epithelium, and bacterial virulence by decreasing production of cytotoxic bacterial enzymes while limiting the mobility of the bacteria by affecting the *pili* and *flagella* [27–30]. Recently, it has been shown in a subanalysis of the BLESS trial that erythromycin was able to reduce expression of *Pseudomonas aeruginosa* quorum sensing genes [31]. Beside its antibacterial effects, macrolides are considered to have anti-inflammatory effects, altering the immune system and airway defense mechanisms.

When the human airways are exposed to inflammatory mediators, macrolides were found to protect against cilia dysfunction, epithelial damage, and mucus hypersecretion. In addition, an important effect of macrolides on the innate immune system is described acting specifically upon both inflammatory mediators and neutrophilic inflammation. Macrolides were found to reduce levels of pro-inflammatory cytokines and chemokines in vitro and in vivo. Neutrophils, the key players of the inflammatory response in chronic airway diseases such as bronchiectasis, are importantly involved in the response to macrolides. Among the processes that have been demonstrated to be influenced by administration of macrolides are neutrophil chemotaxis, degranulation, and adhesion. Culic et al. showed that azithromycin given to healthy volunteers had a neutrophil-degranulating effect, which was reflected in rapid decreases in azurophilic granule enzyme activities in cells and corresponding increases in serum [32]. In another study it has been shown that azithromycin

resulted in leukocyte apoptosis [33]. In patients with COPD, azithromycin resulted in a decrease in blood leukocyte count [34]. A modulating role of macrolides has also been demonstrated for other inflammatory cells, such as B and T lymphocytes and dendritic cells.

17.2 Downsides of Long-Term Macrolide Treatment

17.2.1 Macrolide Induction of Resistance

The risk of long-term administration of macrolide antibiotics is the induction of macrolide resistance. Malhotra-Kumar et al. [35] convincingly showed that even short courses of macrolides rapidly induced macrolide resistance in oropharyngeal streptococci of healthy volunteers. Macrolide resistance can be induced by two mechanisms. The first mechanism induced by the *erm* (B) gene is responsible for alterations of the ribosomal target, which prevents binding and activity of the macrolides. This mechanism is responsible for high-level resistance to macrolides and is the most prevalent resistance mechanism in Europe. The other mechanism, causing low-level macrolide resistance, consists of an active efflux pump, caused by the *mef* (A) gene [6, 24]. The induction of macrolide resistance has also been investigated in the BLESS and BAT trial [5, 24]. In the BAT trial, the rate of resistance was measured in sputum. They found that 53 of 60 pathogens (88%) tested for antibiotic susceptibility in 20 patients in the azithromycin group became macrolide resistant. This was significantly higher than the placebo group where only 29 of 112 pathogens (26%) in 22 patients grew resistant [5]. In the BLESS trial, erythromycin significantly increased the rate of macrolide-resistant commensal streptococcal flora (median change, 27.7%) compared to placebo (0.04%) [24]. Deleterious effects of induction of macrolide resistance have not yet been shown for the individual patient. For instance, patients on long-term macrolide treatment have been shown to have less symptoms and better lung function, irrespective of the presence of macrolide-resistant pathogens. Moreover, in the individual patient, macrolides have been shown to importantly reduce the total number of pathogens.

The danger of widespread use of macrolides lies in the increasing numbers of macrolide-resistant pathogens in the population. Macrolide-resistant pathogens have been shown to cause difficult-to-treat infections in vulnerable hosts such as the immunocompromised. In addition, resistance genes may be transferred to other types of pathogens, and cross-resistance to other antibiotics has been observed. Therefore, the danger of resistance is mainly an induction of population antimicrobial resistance, especially with the widespread use of the long-acting macrolides, as azithromycin [36].

17.2.2 Influence of Long-Term Antibiotics on the Respiratory Microbiome

Wang et al. showed that antibiotics can change the composition of the microbiome [37]. They demonstrated that in patients experiencing a COPD exacerbation, there was an increase in prevalence of gram-negative microorganisms. After the administration of antibiotics, there was a shift from a predominance of gram-negative to gram-positive microorganisms. The administration of long-term antibiotics could potentially induce more definite changes to the respiratory microbiome. This was further corroborated by Rogers et al. In a post hoc analysis of their BLESS trial, they analyzed the change in microbiome composition between the baseline and 48 weeks of erythromycin administration. In patients colonized with microorganisms other than *P. aeruginosa*, long-term treatment of erythromycin caused an increase of culture positive *P. aeruginosa* compared to patients receiving placebo for 48 weeks. No change in respiratory microbiome had been observed in patients who were already colonized with *P. aeruginosa*. Because of this important change in microbiome composition, the authors recommend a careful approach of long-term treatment with erythromycin in patients with bronchiectasis not colonized with *P. aeruginosa* [38].

17.2.3 Induction of Macrolide Resistance in *Mycobacterium Avium* Complex Disease

Due to its positive effects in different respiratory conditions, macrolides are increasingly being used. The main concern encompasses increased macrolide resistance in respiratory pathogens and an increase in oropharyngeal carriage of resistant commensals. Another important concern however is macrolide resistance in *Mycobacterium avium* complex pulmonary disease, as resistance causes a poor prognosis and relapse. It remains to be established whether different treatment regimens or on/off use can prevent resistance appearance. Prior to starting macrolide maintenance treatment, physicians are advised to culture for NTM in their patients.

17.3 Side Effects of Macrolide Treatment

The most prevalent adverse event entails gastrointestinal complaints, but this rarely leads to discontinuation of the treatment as this often is a mild complaint. Other noteworthy side effects are hepatotoxicity, cardiotoxicity, and ototoxicity. The latter is a reversible sensorineural hearing loss, but only rarely occurs at standard azithromycin dosage in bronchiectasis. The majority of adverse events occur due to high serum levels. One study showed that patients who had adverse events had higher serum concentrations and that, when dosage was reduced, side effects fade [39]; however, this dose-dependent relationship between macrolide levels and side effects was not confirmed in a trial of low-dose macrolide treatment [40].

Most adverse effects are reversible and non-life-threatening, with the exception of cardiotoxicity. Macrolides have shown to prolong the QT interval while also inhibiting the metabolism of other pro-arrhythmogenic drugs. Ray et al. showed in a large retrospective observational cohort study that even after 5 days of azithromycin therapy, the use was associated with an increased risk of cardiovascular death and death from any cause [41]. Conversely, large randomized, placebo-controlled trials in stable coronary artery disease patients treated with 600 mg azithromycin weekly showed no increase in mortality [42, 43]. Similar reassuring findings were published by Albert et al. in their large randomized azithromycin trial for prevention of COPD exacerbations [15]. As a solution, Altenburg et al. have suggested that the following patients are at risk for QT prolongation or torsades de pointes: patients older than 80 years, female gender, heart disease, use of other QT prolonging therapies, reduced drug elimination, bradycardia, genetic predisposition, hypokalemia, hypomagnesemia, and a prolonged QT interval before macrolide initiation [44].

As a general rule, we advocate an initial ECG checkup in all patients where macrolide therapy is initiated, with ECG follow-up to evaluate prolonged QT interval, certainly in patients at risk for prolonged QT interval.

Finally, hepatotoxicity has been described for macrolide treatment but rarely leads to fulminant hepatitis or liver failure. One study suggested that azithromycin-induced liver injury occurs within 1–3 weeks after treatment initiation and is predominantly hepatocellular in nature [45]. Although serious hepatic complications are rare, it is common practice in some countries to perform at least one blood analysis to screen for hepatotoxicity at the start of treatment and at the first follow-up outpatient visit.

17.4 Other Long-Term Oral Antibiotic or Anti-inflammatory Strategies

Several other strategies have been hypothesized to be a potential intervention for the treatment of bronchiectasis. Here, we summarize the most important targets and evidence.

17.4.1 Tetracyclines

Tetracyclines are broad-spectrum antibiotics that not only exhibit antibacterial activity but also possess anti-inflammatory properties [46]. More specifically, doxycycline has been hypothesized to inhibit matrix metalloproteinases. Research showed that in CF, doxycycline resulted in a dose-dependent reduction in CXCL-8 and MMP-9 release in lung epithelial cells with minimal cell death [47]. These findings remain to be confirmed in large clinical trials. One recent small trial conversely

showed no influence of doxycycline on sputum myeloperoxydase levels or any other systemic and sputum marker including MMP-8, MMP-9, and CXCL-8 [48]. Although long-term administration of doxycycline 100 mg once daily is often selected as an alternative to chronic macrolide therapy, especially in patients colonized with susceptible pathogens, more research is needed to fully elucidate its effects in bronchiectasis.

An interesting development entails the development of chemically modified tetracyclines (CMT) which own anti-inflammatory properties but are devoid of an antibacterial mode of action. Although they were found to reduce levels of matrix metalloprotease, free radicals, and pro-inflammatory cytokines in small trials of periodontitis patients, to date no studies have investigated their effectiveness in bronchiectasis [49].

17.4.2 Other Antibiotics

Long-term oral antibiotic treatment has been studied, but most studies include only small populations. One study showed slight FVC improvement after 4 months of amoxicillin [50]. A few years later, Currie et al. further investigated the use of amoxicillin (3 g) or matched placebo twice daily for 32 weeks in a double-blind study. The group receiving amoxicillin had less symptoms, had less days away from work, and had a greater reduction in sputum purulence. However, no difference in exacerbation frequency had been observed [51].

17.4.3 Corticosteroids

Corticosteroids are widely used in the obstructive lung diseases asthma and COPD. Inhaled and systemic corticosteroids, along with macrolides, are the most widely investigated anti-inflammatory treatment in bronchiectasis. Here we summarize the evidence and its use in daily practice.

17.4.3.1 Inhaled Corticosteroids

Several trials have looked into the effects of inhaled corticosteroids [ICS]. One of the first trials treated a small number of patients with 1500 μg beclomethasone dipropionate per day and showed a reduction in sputum volume, cough symptoms with small improvements in morning peak flow, and FEV_1 [52]. Later trials with fluticasone 500 μg twice daily showed similar sputum volume reductions and a dampening effect on sputum inflammation but with no effect on lung function and exacerbations [53–55]. In 2009, a Cochrane meta-analysis concluded that there is insufficient evidence to recommend the routine use of ICS in adult stable-state bronchiectasis [56]. More recent trials seem to corroborate these conclusions. ICS (400 μg budesonide twice daily for 6 months) only showed significant sputum eosinophil reduction. However nonsignificant improvements were seen for symptoms, exacerbations, quality of life, and CXCL-8 levels [57].

Overall, ICS might be beneficial in some patients with bronchiectasis, especially on symptoms and sputum volume. However, one needs to take into account that most trials not only had important limitations, but some might have included COPD or asthma patients with bronchiectasis. In general, ICS are not routinely advised in bronchiectasis unless patients have coexisting conditio ns that need ICS (e.g. asthma). In patients where ICS is started; a careful evaluation of its effects is needed.

17.4.3.2 Inhaled Corticosteroid/Long-Acting Beta-Agonist Combination

The combination of an inhaled corticosteroid and a long-acting beta-agonist has been investigated in one small trial with a high risk of bias. The absence of high-quality evidence means that this treatment option shouldn't be started unless there are other coexisting conditions that might benefit from this intervention, such as asthma [58, 59].

17.4.3.3 Oral Corticosteroids

A recent Cochrane review update in 2011 couldn't identify a randomized trial looking at the impact of oral corticosteroids (OCS) in bronchiectasis patients [60]. However, certain etiological subgroups could benefit from OCS, such as patients with allergic bronchopulmonary aspergillosis, asthma, or COPD. This somewhat hampers research into the use of OCS in bronchiectasis as a substantial subgroup of patients have these coexisting conditions. Further research is needed to unravel the effect of long-term OCS in a stable situation and during exacerbations, both in patients with and without the abovementioned comorbid conditions/etiologies. However, one should be very cautious in using OCS considering the serious side effects and the clear lack of evidence.

17.4.4 Neutrophil Elastase Inhibitor

During the vicious cycle, lung inflammation is markedly increased with a predominantly neutrophilic inflammatory profile. Neutrophil elastase, a serine protease, can be found in high concentrations in these neutrophils during active inflammation. The airway inflammatory response triggered by an infection appears to be excessive in relation to the bacterial burden and may persist even after the infection has been controlled. Inhibition of this neutrophil elastase might therefore be an interesting treatment to halt this vicious cycle. Different neutrophil elastase inhibitors are being studied, and currently, results from one molecule have been published. AZD9668 60 mg given orally twice daily for 4 weeks was compared to placebo in patients with bronchiectasis. Significant beneficial changes in FEV_1 and CXCL-8 were observed, but no significant difference had been present for sputum purulence, sputum weight, sputum neutrophils, and sputum neutrophil elastase [61]. Other molecules, such as the neutrophil elastase inhibitor BAY85-8501, are under research as

well [62]. However, larger and longer-term trials are necessary to fully evaluate its effect, specifically on the prevention of exacerbations.

17.4.5 NSAIDs

To tackle the inflammation of the vicious cycle, nonsteroidal anti-inflammatory drugs have been investigated in two small studies. Four weeks of oral indomethacin 25 mg three times a day showed no effect on lung inflammation, sputum volume, and neutrophils, although it showed some marked inhibition of peripheral neutrophil function [63]. A recent Cochrane review reported an older study on the use of nonsteroidal anti-inflammatory drugs. Inhaled indomethacin showed a significant reduction in sputum production compared to placebo and a significant improvement in dyspnea, but failed to show lung function or blood indices differences [64, 65]. More trials with longer duration are needed to fully elucidate the effects of nonsteroidal anti-inflammatory drugs in bronchiectasis, and therefore its routine use cannot be advised, also considering the potential side effects like renal or gastric toxicity.

17.4.6 Statins

Leukotriene receptor antagonists [LRA] are being used in asthma as leukotrienes attract eosinophils and act as a potent bronchoconstricting agent. As they also have a role in neutrophil-mediated inflammation, therefore, they could play a role in the treatment of bronchiectasis. LRA has the potential to reduce mucus secretions, edema, and neutrophilic inflammation [66]. A Cochrane review by Corless et al. however couldn't identify any randomized controlled trial that investigated this hypothesis; therefore it is currently not used in the treatment of bronchiectasis [67].

17.4.7 Leukotriene Receptor Antagonists

Statins have shown to change neutrophil recruitment in both animals and humans. They enhance the formation of extracellular DNA traps by macrophages within the lung while also reducing neutrophilic infiltration and chemokine production. Previous research in CAP showed a 30-day mortality reduction in patients taking statins combined with antibiotics [68]. In bronchiectasis, 6 months of 80 mg atorvastatin improved cough, lowered CXCL-8 levels, and increased the number of apoptotic neutrophils in the airways, suggesting lowered inflammation. However, no significant reduction in exacerbations had been observed. Moreover, patients taking 80 mg of atorvastatins had significantly more side effects [69]. A second trial with atorvastatin for 3 months in chronically *P. aeruginosa*-infected patients also showed reduced serum inflammation and improved quality of life but no improvement in

cough [70]. These findings generally lead to the conclusion that routine use of statins as an anti-inflammatory treatment cannot be recommended.

17.4.8 Methylxanthines

Methylxanthines are speculated to be a possible treatment for bronchiectasis as they might not only improve respiratory muscle strength but also may act as an anti-inflammatory agent. However, to our knowledge, up to now no trials have been performed. Therefore, their use in bronchiectasis cannot be recommended [71].

17.4.9 CXCR2 Antagonists

As knowledge on the nature of the inflammation in bronchiectasis is accumulating, an increasing number of potential targets are unraveled. Many elements in the inflammatory cycle are potential targets for further therapies. One example is the CXCR2 antagonist AZD5069. It is known that CXCL-8 mediates neutrophil infiltration and activation in the lung, causing its chemokine receptors CXCR1 and CXCR2 to be a potential target for anti-inflammatory treatment [72]. AZD5069, a CXCR2 antagonist, was administered orally at a dose of 80 mg twice daily for 28 days. The results showed that sputum neutrophils were decreased when given CXCR2 antagonist compared to placebo without observing improvement in clinical outcomes [73]. Further studies are needed to fully evaluate its effect.

Conclusion

Macrolides have been shown to be very effective as maintenance treatment in patients with bronchiectasis in preventing acute exacerbations. This could be explained by their antibacterial and immunomodulatory properties. Prior to the initiation of macrolide treatment, one has to consider certain important remarks. First, macrolides are known to induce bacterial resistance, and its benefits in patients with frequent exacerbations should be weighed against its potential harm in causing bacterial resistance. Treating physicians should especially be very vigilant for non-tuberculous mycobacteria and certainly screen their patients for its presence prior to initiation of macrolide maintenance treatment. Second, patients with a known cardiac history should be screened and followed on initiation of macrolide treatment as macrolides are known to cause prolonged QT intervals. The current bronchiectasis guidelines recommend the use of macrolide maintenance treatment in bronchiectasis patients with three or more exacerbations/year, and ongoing research aims at discerning other predictors of a favorable response to macrolides in order to further limit maintenance treatment to the patient groups which are expected to benefit the most. Azithromycin is the macrolide with the strongest track record in clinical trials and is therefore the macrolide of choice for maintenance treatment of

bronchiectasis at the moment. No solid evidence exists in favor of a certain dosage, dosing frequency, or treatment duration, but azithromycin dosages of 250 mg once daily and 500 mg thrice weekly are commonly used, inspired by the BAT and EMBRACE trial.

Other anti-inflammatory treatments shouldn't be prescribed regularly. Some of them might be beneficial in specific clinical context, but need careful consideration. There are however new treatments in development, showing promising results. Further research is needed to expand the therapeutic arsenal and tackle the anti-inflammatory component of bronchiectasis.

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Airway Clearance in Bronchiectasis

18

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18.1 Introduction

The chapter describes the bronchiectasis pathophysiology that informs and influences airways clearance techniques (ACT) and provides an overview of the aims of ACT and current practices in bronchiectasis. The main physiological mechanisms underlying ACTs as well as the current evidence base are detailed. Mucoactive drugs are discussed particularly in terms of dose, delivery device/route and timing with ACT to facilitate airway clearance. Recognising that the evidence base for ACT in bronchiectasis is low with few high-quality studies, a review of the outcomes used in randomised crossover and controlled trials (RCTs) in bronchiectasis has been included. This has also focused on the utility and feasibility of the commonly used endpoints as well as the potential clinical endpoints that could be considered for use in future ACT clinical trials.

18.2 Bronchiectasis Pathophysiology that Informs and Influences ACTs

When applying ACTs, it is important to have an understanding of the factors that affect mucus transportability and expectoration including: impaired mucociliary clearance (MCC); infection, inflammation and cough. Other chapters will provide

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more in-depth discussions on the pathophysiology, in this chapter we have focused on the bronchiectasis pathophysiology in the context of how it informs and influences ACT.

18.2.1 Impaired Mucociliary Clearance (MCC)

The body's MMC system is an important lung defence mechanism consisting of airway surface liquid comprising of mucus and periciliary layers, ciliary epithelium and a cough mechanism [1]. In healthy people, cilia beat at a mean frequency of between 11–13 Hz [2] propelling mucus proximally up the airways at a rate of between 4–5 mm/min [3, 4]. MCC requires highly coordinated and synchronised beating of cilia across multiple ciliated cells. Autoregulation of ciliary movements is a fundamental mechanism governing ciliary activity. Ciliary autoregulation responds to disruption of the periciliary layer induced by small changes in overlying mucus, but fails when mucus load is excessive [5]. Furthermore, a lack of motile cilia could be present in some bronchiectasis patients. Studies in mice suggest that a lack of a key protein (IFT88) in is necessary to form motile cilia and therefore plays an important role in controlling airway function and structure. When this protein is depleted, there is a decrease in cilia beat frequency [6].These cilia defects have been shown to be independent of sputum purulence or the presence of bacteria such as *Pseudomonas aeruginosa* [7, 8].

Mucus is a viscoelastic gel consisting in water and high-molecular weight glycoproteins called mucins mixed with serum, cellular proteins and lipids. Sputum is the expectorated mucus mixed with inflammatory cells, cellular debris, DNA as well as bacteria [2]. The rate of clearance is strongly influenced by the mucus hydration state, rigidity and viscosity to elasticity ratio [9, 10]. Usually in health, airway secretions are cleared by MMC as part of the normal host response. In bronchiectasis the mucociliary transport system is impaired. This is due to a combination of one or more of the following conditions: dehydration of the periciliary layers, absence of lubricant activity which prevents adhesion of mucus to airway surfaces [5], an inherent defect within the cilia [7] or specific antibody deficiencies. The underlying aetiology of bronchiectasis disease influences the contribution of each of these factors to impaired mucociliary clearance.

Structural changes in bronchiectasis airways including abnormally dilated airways, allows mucus to pool, making it more difficult to clear by normal MCC and cough mechanisms. Bacteria can adhere to the mucus and proliferate resulting in large bacterial counts in the sputum. As a result, a host neutrophilic response ensues and the by-products of the ineffective inflammatory response can result in further bronchial wall damage, continued infection and a perpetuated inflammatory response termed a "vicious circle". Knowledge of the aetiology of the disease can help to understand the primary contributing factors to the "vicious circle" (i.e. post infection or immune deficiency).

In bronchiectasis the sputum can also be more purulent and adhesive compared with other chronic respiratory diseases, e.g. chronic obstructive pulmonary disease

(COPD) and healthy subjects [4]. This purulent mucus has higher contact angle, increase forces of attraction and cohesion between molecules that result in changes in mucus conformation and rheological profile [3]. As a result, bronchiectasis secretions have lower transportability and impaired proximal movement during cough and/or ACTs. Once the lung defence system is breached, it is susceptible to more infection and inflammation which results in further airway damage and increasing severity of bronchiectasis [6].

18.2.2 Cough Transportability

Evidence from in vitro studies using a mechanical stimulus highlight the potential role of how changes in pressure and/or airflow influence cilia beat frequency and hydration of the airway cell surface [9, 11–13]. In vitro studies have demonstrated that the mechanism of action of increased cilia beat frequency may be due to mechano-sensitive ATP release in the lungs and elevation in Ca^{2+} concentrations when a mechanical stress of the airways is produced by changes in pressure and/or airflow shearing [11].

Coughing is a normal reflex defence mechanism used to clear excessive secretions down to the 7th or 8th generation of airways [14]. In health, a typical cough consists of a deep inspiration followed by closure of the glottis. High intrathoracic pressures (up to 300 mmHg) build up, resulting in a high explosive, turbulent expiratory flow rate that may exceed 500 L/min when the glottis is opened. During this time, dynamic compression of the airways occurs resulting in an increase in velocity and kinetic energy which enhances the proximal movement of mucus, overcoming the shear force of mucus attached to the airway walls. Distal to the regions where the airways are compressed, there may be a collapse of the airways, especially when airway instability is present [15]. Cough is an effective method of clearing secretions from the larger airways in healthy subject. However, in bronchiectasis bronchial wall instability may result from recurrent compression of the airways during cough, thus reducing expiratory flow and limiting the effectiveness of the cough [16]. Therefore ACTs should be used as the primary method of mobilising secretions from the middle and small airways to the larger airways. At this stage one effective cough can be used to clear secretions from the larger airways, thereby preserving the integrity of the larger airways.

18.3 Prescribing ACT Across the Disease Trajectory

There is general agreement that airway clearance is a key component in the management of bronchiectasis, and therefore all patients with bronchiectasis should be screened for symptoms that may benefit from the prescription of ACT. As presentation of bronchiectasis changes, an increase in frequency and change in duration and/or type of ACT may also be beneficial [16]. Prescription of ACT for patients with

bronchiectasis is based on presence of one or more of the following screening criteria: new diagnosis of bronchiectasis or commencement of new treatments such as airway pharmacotherapy (mucoactive therapies). Evidence and/or expert opinion suggests that patients with the following signs and symptoms of bronchiectasis may benefit from ACT.

- Patients with a chronic productive cough [16] (a productive cough lasting ≥8 weeks).
- Patients with a non-productive cough who may need to use ACTs during pulmonary exacerbations [17].
- Patients who may need to minimise an irritating non-productive cough [16].
- Current pulmonary exacerbation or unstable symptoms.
- Evidence of ventilation homogeneity as shown on LCI which can indicate early disease [18].
- Evidence of secretions and/or mucus plugging, e.g. on a recent high-resolution CT scan (HRCT) [16]; other assessments such as chest X-ray; auscultation and spirometry may be useful.
- More severe disease, e.g. patients with more frequent exacerbations or with higher Bronchiectasis Severity Index Score (BSI) and/or Bronchiectasis Aetiology and Comorbidity Index Score (BACI) [19].

The short-term goals of ACT in patients with bronchiectasis are to: facilitate sputum expectoration during treatment sessions and reduce sputum production for the remainder of the day, increase sputum expectoration in the short term thereby limiting bacterial burden and decreasing inflammation in the airways as well as reduce breathlessness, wheeze and improve ventilation.

Longer-term goals are targeted at reducing further airway damage by halting vicious cycle of bacterial colonisation and subsequent inflammation, reducing time to next pulmonary exacerbation, reducing severity of pulmonary exacerbations and incidents of hospitalisation for exacerbations, reducing chronic cough, and improving exercise tolerance and physical functioning and health-related quality of life. It is important to consider these goals in terms of informing the choice of clinical endpoints within ACT clinical trials.

18.4 Airway Clearance Techniques (ACTs) Prescribed in Bronchiectasis

Over the past few years, there has been increased focus on ACTs in the treatment of bronchiectasis. However, the evidence to support their use has been largely empirical with relatively few controlled studies. The British Thoracic Society (BTS) and other authors have attempted to provide guidelines on the management of bronchiectasis, based on published studies or consensus views [16]. It is recommended that patients should be possibly encouraged to be independent with their chosen ACT.

18.4.1 Airway Clearance Techniques (ACTs)

The European Bronchiectasis Data Registry (EMBARC) contains current data on approximately 5000 patients with bronchiectasis. It reports that only 45% of data registrants perform an ACT regularly. The underlying premise for an ACT to be effective is its need to assist the body's natural MCC system to transport secretions proximally up the airways. Historically, positioning was used primarily for drainage by relying on gravity, combined with percussion of the chest wall to achieve this MCC [20, 21]. However the literature does not support the use of postural drainage. Newer ACTs rely on two overriding physiological principles described in detail by coauthors in a separate publication as summarised in Table 18.1 [22]: firstly, a mechanism to allow air to move behind obstruction and ventilate the regions distally and, secondly, modulation of expiratory airflow, in such a way as to propel secretions proximally up the airways. To propel secretions proximally, the peak expiratory flow rate (PEFR) must exceed 30–60 L/min to overcome the adhesive strength by which the mucus is attached to the airway interface and the PEFR must exceed the peak inspiratory flow rate (PIFR) by at least 10% to create an expiratory airflow bias [23].

In terms of evidence base, only a limited number of clinical trials have been conducted in bronchiectasis, and many of these are single treatment studies (Table 18.2). A review by Snijders et al. of ACT in bronchiectasis also highlighted the lack of longer-term studies [24]. Single intervention studies (i.e. a comparison between one treatment session of a specific ACT versus one treatment session of another ACT) or evidence of effectiveness within a specific intervention group are useful in providing information on patient acceptability and side effects in order to justify a longer-term trial to establish efficacy. However, the authors express caution in using the results of single intervention studies or within group differences as the evidence base for ACTs in bronchiectasis. For the purposes of this chapter, we have focused on the evidence base from longer-term comparative studies that have incorporated clinical and/or surrogate endpoints.

18.4.2 Active Cycle of Breathing Techniques (ACBT)

Based on current data from the EMBARC database, 55% of patients report performing ACBT as their ACT of choice. ACBT consists of breathing control, interspersed with thoracic expansion exercises and the forced expiration technique comprising of huffing combined with breathing control [25]. Thoracic expansion exercises allow air to move behind the secretions using collateral ventilation and interdependence. It may incorporate a 3 s breath hold which further alters time constants, allowing more time for the pressure gradient to equalise in the obstructed units to further enhance airflow to these areas. ACBT also incorporates huffing which is the main driver and relies on the use of EPP. The PEFR, with a huff at high lung volume, is similar to a cough demonstrating that the increase in airflow linear velocity is sufficient to promote proximal movement of secretions [26]. The breathing level at

Table 18.1 Physiological basis for each ACTs [22]

		Ventilation			Expiratory	Airflow	
	Interdependence	Collateral ventilation (CV)	Breath hold	Huffing	PEFR/PIFR > 1.1	PEFR > 30–60 L/min	Oscillation
ACBT	Thoracic expansion exercises utilises interdependence	Thoracic expansion exercises utilises CV	Sometimes used with this technique if hypoventilating	Uses forced expirations at different levels of inspiratory volume	Ratio = 2.8	Average 302 L/min with huffing	No
Autogenic drainage	No	Yes with breath hold	Uses 3 s breath hold with each breath	No	Yes, emphasis is on slow inspiration and increased velocity on expiration	40–70 L/min. Depends on level of breathing and degree of airway obstruction	No
PEP	No	As a PEP is maintained within the airways during 12–15 breaths, use of CV is maximised	No	Used at end of each cycle of 12–15 breaths	No (Ratio = 0.47)	No average 26 L/min	No
Flutter	Oscillations between 3 and 5 Hz may play a role, but frequency used in flutter is >5 Hz	Yes with breath hold	Uses 3 s breath hold with each breath	Used at end of each cycle of 8–10 breaths	Ratio = 1.15	Average 68 L/min	2–32 Hz most often uses 6–26 Hz

Acapella	Oscillations between 3 and 5 Hz may play a role, but frequency used in Acapella is >5 Hz	As a PEP is maintained within the airways during 12–15 breaths, the use of CV is maximised	No	Used at end of each cycle of 12–15 breaths	No (Ratio = 0.64)	Average 35.4 L/min within PEFR, but would depend on viscoelastic and viscosity properties of secretions	10–18 Hz
HFCWO	Oscillations between 3 and 5 Hz may play a role, but frequency used in HFCWO is >5 Hz	No	No	Interspersed with HFCWO	Yes, expiratory flow rate is much higher than inspiratory flow rate	Average 120 L/min	5–25 Hz

ACBT active cycle breathing techniques, *AD* autogenic drainage, *PEP* positive expiratory pressure, *HFCWO* high-frequency wall oscillation, *CV* collateral ventilation, *PEFR* peak expiratory flow rate, *PIFR* peak inspiratory flow rate. *Interdependence*—During inspiration, the expanding alveoli exert forces on the adjacent alveoli which enhance the recruitment of lung units. *Collateral ventilation*—With increasing inspired volumes, the resistance to airflow within the canals of Martin, channels of Lambert, and pores of Kohn (between the bronchioles and alveoli) decreases, and air flows through these channels to enhance expiratory flow behind the secretions

Table 18.2 Randomised crossover trial and randomised controlled trials in patients with bronchiectasis

Author	Study design length of treatment	No of patients	Treatment groups	Key clinical and surrogate endpoints (pulmonary exacerbation, HRQoL, lung function, sputum) and physiological measures
Eaton [38]	RCT crossover	36 stable adult bronchiectasis patients	G1: Flutter G2: ACBT G3: ACBT with postural drainage (ACBT-PD)	• The mean difference in total wet weight sputum was significantly greater for ACBT-PD compared to flutter ($p < 0.001$) and ACBT ($p < 0.001$)
	Single treatment			• Most patients (44%) preferred flutter compared with ACBT-PD (33%) or ACBT (22%)
Figueiredo [39]	RCT crossover	8 stable adult bronchiectasis patients	G1: Sham Flutter (control group) G2: Flutter	• Significantly greater volume of sputum produced in G2 versus G1 ($p < 0.05$)
	Single treatment			• Significant decrease in airway resistance in G2 versus G1 ($p < 0.05$)
Guimaraes [40]	RCT crossover	10 stable adult bronchiectasis patients	G1: Control—15 min seated and coughing only	• Lung function tests of FRC, RV and TLC decreased significantly with G2 and G3 compared to G1 ($p < 0.05$)
	Single treatment		G2: ELTGOL—15 min and coughing	• Sputum dry weight was significantly greater with G2 versus G3 or G1 ($p < 0.05$)
			G3: Flutter—15 min, no huffing, coughing only	
Herrero-Cortina [29]	RCT crossover	31 stable adult bronchiectasis patients	G1: Autogenic drainage	• No significant change in lung function
	3 treatment sessions		G2: ELTGOL—15 min and coughing	• Significant increase in Leicester Cough Questionnaire in all groups, but there was no difference between groups ($p = 0.6$)
			G3: Temporary positive expiratory pressure	• Significantly greater sputum weight during physiotherapy treatment produced in G1 and G2 versus G3 ($p < 0.05$)
				• No significant difference in overall expectoration in the 24-h period between groups ($p = 0.8$)

Murray [34]	RCT crossover 3 months	20 stable adult bronchiectasis patients	G1: Control, no treatment G2: Acapella in sitting	• No significant change in pulmonary exacerbation frequency • Significant increase in Leicester Cough Questionnaire ($p = 0.002$) and SQRQ ($p = 0.005$) in G2 versus G1 • No significant change in lung function • Significant increase in 24 h sputum volume in G2 versus G1 ($p = 0.02$) • Significant improvement in exercise capacity in G2 versus G1 ($p = 0.001$) • No significant change in sputum bacterial load
Naraparaju [41]	RCT crossover Single treatment	30 stable adult bronchiectasis patients	G1: Inspiratory muscle trainer G2: Acapella	• Significantly greater volume of sputum produced in G2 versus G1 ($p < 0.05$) • Patients preferred Acapella ($p = 0.03$)
Nicolini [42]	RCT 15 days	30 stable adult bronchiectasis patients	G1: HFCWO G2: Patients usual ACT G3: No treatment	• Significant improvement in HRQoL in G1 and G2 versus G3 ($p = 0.001$) • Significant improvement in FVC and FEV_1 in G1 and G2 versus G3 ($p < 0.05$) • Significant increase in sputum volume with both G1 ($p = 0.001$) and G2 ($p = 0.004$) compared to control, but significantly more with G1 ($p = 0.01$) • Significant improvement with blood inflammatory markers with G1 ($p < 0.0019$)
Patterson [43]	RCT crossover Single treatment	20 stable adult bronchiectasis patients	G1: ACBT in 2 PD positions G2: Acapella with huffing in PD positions	• No significant difference in lung function between groups • No significant difference in sputum weight between groups • Patients preferred Acapella

(continued)

Table 18.2 (continued)

Author	Study design length of treatment	No of patients	Treatment groups	Key clinical and surrogate endpoints (pulmonary exacerbation, HRQoL, lung function, sputum) and physiological measures
Patterson [44]	RCT crossover	20 stable adult bronchiectasis patients	G1: ACBT in 2 PD positions	• No significant difference in lung function between group
	Single treatment		G2: Test of incremental respiratory endurance—6 sustained maximal inspiratory pressure manoeuvres followed by huffing	• Sputum weight significantly greater with G1 ($p = 0.01$)
Patterson [45]	RCT	20 adult bronchiectasis patients acute exacerbation	G1: Acapella with huffing in PD positions	• No significant difference in lung function between groups
			G2: Usual ACT routine (ACBT = 9, PEP = 1)	• No significant difference in sputum volume between groups
	10–14 days			• No significant difference in oxygenation or breathlessness
Paneroni [46]	RCT crossover	22 adult bronchiectasis patients, acute exacerbation	G1: CPT—forced expiration, postural drainage, percussion and vibration, 3 positions, 10 min each positions	• No significant difference in wet or dry weight sputum or sputum volume between groups
	Single treatment			• Significant decrease in respiratory rate with G2 compared with G1
			G2: Intrapulmonary percussive ventilation (IPV)	• Significant decrease in heart rate pre and post within both groups
				• No significant difference in heart rate, dyspnoea or SpO_2 between groups
Sutton [47]	RCT crossover	8 adult bronchiectasis patients	G1: PD with huffing	• No significant difference in lung function between group
			G2: Control, no treatment	
	Single treatment			• Significant improvement in sputum weight with G1 versus G2 ($p = 0.01$)
Syed [48]	RCT crossover	35 stable adult bronchiectasis patients	G1: ACBT	• Significant difference in FEV_1/FVC pre and post treatment in both groups ($p < 0.03$)
			G2: Percussion, vibration, breathing techniques	• No significant difference in lung function between groups
				• No significant difference in sputum weight or volume between groups
				• Patients preferred G1 with greater comfort

Thompson [27]	RCT crossover	17 stable adult bronchiectasis patients	G1: Flutter with huffing	• No change in HRQOL
			G2: ACBT	• Statistically significant improvement in FEV_1 with G1
				• No significant difference in weekly wet sputum weight
				• Patients preferred G1 treatment
	4 weeks			• No significant change in flow rate or breathlessness
Cecins [49]	Crossover	19 stable adult bronchiectasis patients	G1: ACBT with PD	• No significant difference in lung function between groups
	Single treatment		G2: ACBT no PD	• No significant difference in sputum weight between groups
				• Breathlessness was significantly greater with ACBT with PD group
				• Patient preference was for ACBT no PD

G1 group 1, *G2* group 2, *HRQoL* health-related quality of life questionnaire

which the huff is performed and the strength of the huff are both adjusted to allow the EPP to occur where the secretions are located.

In terms of supporting evidence for the use of ACBT, there are two studies which have interventions longer than single interventions (Table 18.2). No studies compare ACBT to "no treatment" and comparisons with other ACTs e.g. Acapella or flutter show no difference in key outcomes (health related quality of life (HRQoL), lung function and sputum [27].

18.4.3 Autogenic Drainage (AD)

Based on current data from the EMBARC database, approximately 15% of registrants used AD. In AD the expiratory flow rate is modulated to maximise airflow velocity avoiding dynamic compression of the airways. Expiration is performed at three different levels within the lung volumes (unsticking phase, collecting phase, and evacuating phase). In a study with patients who had obstructive lung disease performing AD, the expiratory airflow varied between 40–70 L/min, depending on lung volume and level of breathing, thereby moving secretions proximally [28]. A slow inspiratory flow rate is necessary to create an expiratory flow rate bias by at least 10%. Ventilation to obstructed lung regions is achieved by using a 3 s breath hold on inspiration during tidal volume breathing, utilising the collateral ventilation channels [15]. AD is usually performed in an upright position, but it can also be performed in alternate side-lying or supine to enhance ventilation to specific lung regions.

In terms of supporting evidence for the use of AD, there is one study which was longer than a single intervention (Table 18.2). In that study, AD and ELTGOL was compared to a control group of patients performing a non-specific technique. Both AD and ELTGOL resulted in significantly greater sputum compared to the control group [29] (Table 18.2).

18.4.4 Positive Expiratory Pressure (PEP)

Based on current data from the EMBARC database, 45% of registrants reported using airway clearance devices such as PEP mask. PEP therapy is a flow regulating technique, consisting of breathing against an expiratory resistor to create a PEP of between 10 and 20 cms H_2O. This is combined with huffing and coughing [30]. Whilst breathing through a PEP device in a closed system over 12–15 breaths, the functional residual capacity (FRC) level is increased. The airways are splinted open allowing air to move behind secretions via collateral channels [31, 32]. Whilst ventilation is improved through the use of PEP, the expiratory airflow necessary to mobilise secretions proximally is not achieved as PEP only has a PEFR/PIFR of 0.47 [33]; therefore PEP needs to be combined with a manoeuvre such as huffing or autogenic drainage.

To date there have been no studies longer than a single intervention exploring PEP in bronchiectasis.

18.4.5 Oscillating PEP Using Flutter and Acapella

From the EMBARC database, 45% of registrants reported using airway clearance devices such as oscillating PEP devices such as the Flutter and Acapella. Oscillating devices combine positive expiratory pressure with oscillations on expiration. The most commonly used oscillating PEP devices are the Acapella and the Flutter [34, 35]. Both provide similar frequency of oscillations within the range necessary to decrease the viscoelastic and spinnability properties of mucus, thereby improving mucus clearance [36]. Flutter oscillates with frequencies 6–26 Hz, with average PEP pressures of 18–35 cms H_2O. Acapella oscillates with frequencies of 10–18 Hz, with an average pressure between 10–25 cms H_2O [37]. The physiological mechanisms underpinning Acapella and Flutter are different (Table 18.1). The Acapella can be used similar to a PEP mask, with the added advantage of oscillation. FRC is increased whilst breathing through the Acapella, increasing alveolar gas mixing to obstructed lung units via collateral ventilation channels and decreasing the inhomogeneity of ventilation. Similar to PEP, with the Acapella, the expiratory flow bias is insufficient to mobilise secretions centrally (PEFR/PIFR ratio of 0.64) [33]. Therefore the Acapella needs to be combined with huffing to assist in mucociliary clearance. The Flutter device only allows exhalations to be performed through it, thus FRC is not increased. To compensate for the ventilatory asynchronism, inspiration is followed by a 3 s breath hold. Exhaling through the flutter device produces an expiratory flow bias of PEFR/PIFR 1.15 which is sufficient to mobilise secretions. As the PEFR with a huffing manoeuvre is the same as a cough (302 L/min with a huff versus 280 L/min with a cough) [33], huffing is usually added at the end of each breathing cycle with both the Acapella and the Flutter to assist in mobilising secretions proximally up the airways.

In terms of supporting evidence for the use of oscillating PEP, there is one study which had was longer than a single intervention (Table 18.2). Murray et al. compared Acapella to no treatment in stable adult bronchiectasis patients over a 3 month period [34]. There was no change in pulmonary exacerbation frequency, or pulmonary function. There was significant increases in HRQoL, sputum volume and exercise capacity for the patients performing Acapella compared to the control, demonstrating some proof of concept on the effectiveness of ACTs in bronchiectasis.

18.4.6 ELTGOL

From the EMBARC database only a few reported using ELTGOL. ELTGOL is a technique and has recently been described in several studies on the treatment of bronchiectasis, and although more studies are needed to establish its efficacy, the inclusion of the technique in this overview is justified. ELTGOL comes from the French term, “lexpiration lente totale glotte ouverte en infralateral”, which means a slow total expiration performed with the glottis open in a lateral decubitus position [32]. This technique uses similar breathing manoeuvres as those used in the

unsticking phase of autogenic drainage. Both AD and ELTGOL use the slow expiratory flow to mobilise secretions without causing airway compression. However the PEFR threshold necessary to mobilise secretions has not been established in ELTGOL. ELTGOL uses positioning to increase ventilation to the obstructed lung by placing it in the dependent side-lying position, whereas AD uses both positioning and a 3 s pause at the end of inspiration to enhance ventilation.

In terms of supporting evidence for the use of ELTGOL, there is one study which was longer than a single intervention (Table 18.2). Herrero-Cortina compared ELTGOL to AD and T-PEP technique (a less well-known technique) and found that there was a significant difference in sputum weight in ELTGOL compared to T-PEP [29]. There was no between group difference in HRQoL or Leicester Cough Questionnaire.

18.5 Evidence for the Use of Airway Clearance Techniques

In summary the evidence supporting ACTs in BE is very limited. As a result, most of the evidence supporting the use of ACTs in the treatment of bronchiectasis has been extrapolated from the CF literature. The authors express caution when projecting findings from airway clearance studies in CF patients to bronchiectasis patients, who have a different aetiology, pathophysiology and demographics.

18.6 Mucoactive Drugs to Facilitate Airway Clearance

Mucoactive drugs to facilitate airway clearance can broadly be characterised into several major groups based on their potential mechanism of actions [50].

- *Expectorants*: drugs that induce discharge or expulsion of mucous from the respiratory tract. Typically requires coughing action to loosen and bring up the mucous from the lungs or upper respiratory tract. Examples include hypertonic saline.
- *Mucoregulators*: drugs that regulate mucous secretion or interfere with the DNA/F-actin network. Examples include carbocisteine.
- *Mucolytics*: drugs that decrease mucous viscosity. Examples include N-acetylcysteine.
- *Mucokinetics*: drugs that increase MCC by acting on the cilia. Also referred to as cough clearance promoters. Examples include bronchodilators.

Research evidence and guidelines in bronchiectasis [50] suggest that mucoactive medications can facilitate mucociliary clearance, and so consideration should be given to these when prescribing ACT in order to optimise overall treatment effectiveness. Due to their mechanism of action, they are likely to have a role early in the disease trajectory to facilitate MCC and potentially slow progression of bronchiectasis disease as well as later in the disease trajectory when symptoms are increased.

As many patients can be hyperresponsive to airway pharmacotherapy including mucoactives, a drug response assessment (DRA) (often known as a challenge test or a bronchoconstrictor trial) should be carried out where there is pre-existing evidence that hyperresponsiveness is a potential side effect of a specific mucoactive medication. They should be carried out by a competent individual in a hospital setting where emergency treatment can be given if required. A generic DRA is generally acceptable, and a template has been developed by the Association of Chartered Physiotherapists in Cystic Fibrosis (ACPCF) [51]. Others also have specific drug response assessment templates, for example, mannitol [52, 53]. Drug response assessments should be carried out in a hospital setting where emergency treatment can be given if required. EMBARC and the BTS audit have highlighted that mucoactive therapies are infrequently used [54].

The most frequently used are oral mucoactives with data indicating that less than 15% use carbocisteine in Europe(EMBARC), and available data in the UK suggests that around 30% used carbocisteine. Carbocisteine is a mucoregulator, and its mechanism of action is via metabolism of mucus-producing cells, antioxidant and anti-inflammatory effects and modulates mucus production. The evidence base for carbocisteine in bronchiectasis is poor [55], and it's likely that its reported use in bronchiectasis is based on a large number of studies conducted in COPD. A meta-analysis within this Cochrane review and the majority of the primary studies were able to record a significant reduction in exacerbations over a 1-year time period in patients taking carbocisteine compared to placebo [56].

Data from the EMBARC database indicates that less than 10% patients are prescribed HTS, and this is similar to BTS audit data. Hypertonic saline is classified as an expectorant, and its mechanism of action is via increased secretion volume and/or hydration [50]. The evidence base for HTS in bronchiectasis is limited to a small number of audits, randomised crossover studies [57, 58] and one randomised controlled trial which did not demonstrate any differences between HTS and isotonic in a 1-year study. Over a 1-year period, this study showed that both treatment groups resulted in a very large drop in exacerbation frequency over the year of the study and also quality of life improved in both groups with no difference between groups. There are a number of reasons that may explain the results of this study, and it's likely that isotonic saline comparator group was not a placebo but was actually an active intervention group. Also these patients had relatively mild disease, and it is not clear how HTS was coordinated with ACT. HTS is a relatively cheap mucoactive, and the data to date does justify further study to ascertain the role of HTS in the management of impaired MCC [59].

EMBARC data indicates that deoxyribonuclease (DNase) is prescribed for a small proportion of patients (less than 2%). DNase breaks down the DNA released at the site of infection by the neutrophils making sputum less viscid and therefore easier to expectorate. On the basis of one high-quality double-blind RCT [60] which demonstrated patients given DNase had higher exacerbation and hospitalisation rates, more rapid lung function decline key guidelines recommended that DNase should not be used as a mucoactive in bronchiectasis.

The reasons for this negative finding are unclear, but it is notable that the population was older, weaker and questionably less likely to do airway clearance and may have been unable to clear the sputum from their peripheral airways.

The EMBARC data in less than 1% of patients ($N = 4908$) use mannitol, and this is unsurprising as mannitol failed to be approved by NICE in bronchiectasis. Mannitol is categorised as an expectorant, and whilst the exact mechanism of action is unknown, inhaled mannitol may change the viscoelastic properties of mucus, increase the hydration of the periciliary fluid layer and contribute to increased mucus clearance of the retained secretions through mucociliary activity. Productive cough can contribute to sputum clearance. The early evidence to support the use of mannitol has been the subject of recent reviews which highlighted that this was a promising mucoactive treatment in bronchiectasis [61]. Unfortunately a 12-week phase 3 clinical trial failed to find a significant difference in quality of life between mannitol and placebo, and this was followed by a subsequent phase 3 clinical trial which failed to meet a significant difference between mannitol and placebo in its primary endpoint of rate of exacerbations, albeit that time to next exacerbation was higher in the mannitol group. On the basis of these two trials, mannitol failed to receive licence for bronchiectasis [62, 63].

Bronchodilators are mucokinetics and their mechanism of action is via improved cough clearance by increasing expiratory flow and reversing airflow obstruction. The doses and deliver device (either inhaler or nebuliser) for bronchodilators are dependent on the specific drug prescribed. Although bronchodilators (both short- and long-acting beta agonists, SABA and LABA) are commonly used in the management of bronchiectasis where airflow obstruction is present, there appears to be no high-quality evidence to support their use in this condition although they may have a more defined role in the management of patients with coexistent asthma or COPD, but there is at present no clinical trial data to support this strategy beyond the evidence that exists independently for asthma and COPD [64].

The detail of how each mucoactive drug is used in terms of dose, delivery device/route is summarised in Table 18.3.

In summary the physiological mechanism of action of mucoactive drugs suggests that these drugs have a role in throughout the disease trajectory of bronchiectasis. Sputum retention is one of the most burdensome symptoms of bronchiectasis, and conversely airway clearance is considered by patients one of the most burdensome treatments. Careful consideration of the timing of these drugs with airway clearance is likely to optimise MCC. Future research is needed to determine the most effective mucoactive drugs in bronchiectasis and how they can be used to optimise airway clearance, as well as which subgroups of patients they are likely to have most benefit in.

18.7 Endpoints for Airways Clearance

Sputum expectoration, pulmonary exacerbations and QOL have been highlighted by patients as most important endpoints for ACT in bronchiectasis [17], and this is generally supported by other publications including a Cochrane review and

Table 18.3 Mucoactive drugs in bronchiectasis

Mucoactive	Drug response assessment (DRA)	Timing with ACT/other medications	Dose	Delivery device/ breathing pattern	Side effects
Oral: carbocisteine	Not required	• No guidance. For carbocisteine the maximum concentration in serum is at 2 h (range 1–3) post dose • No rationale for timing with other meds	• Usual adult dose at the beginning of treatment is 2250 mg daily (2 × 375 mg capsules three times a day) until improvement. Dose reduced to 1500 mg daily (1 × 375 mg capsule four times a day)	• Not relevant	• Used with caution in those with a history of peptic ulceration because they may disrupt the gastric mucosal barrier
Hypertonic saline	Yes	• Has immediate action so HTS used prior to ACT (can be administered during ACT if technology permits) • If bronchoconstriction on DRA (or routinely used SABA) considers SABA prior to HTS inhalation	• 6% or 7% HTS, 5 ml ampules are available commercially • To be taken twice daily (up to four times daily)	• Traditional jet nebulisers (e.g. Pari LC jet nebuliser or equivalent), intelligent nebulisers (I-neb/ eFlow devices) are smaller, quicker devices that give improved deposition of medications and reduce inhalation time to less than 5 min • Tidal breathing interspersed with larger inspiratory volumes to optimise deposition	• May cause chest tightness • Salty taste

(continued)

Table 18.3 (continued)

Mucoactive	Drug response assessment (DRA)	Timing with ACT/other medications	Dose	Delivery device/ breathing pattern	Side effects
DNase	Not required	• Unclear usually inhaled 30 min prior to ACT in order to improve small airway patency. Many patients often direct timing of DNase to achieve optimal personal benefit in terms of perceived ease of airway clearance • There are no specific recommendations as this product is not recommended. In CF a gap of 1 hour or greater is OFTEN recommended between DNase and antibiotics or antifungals	• Usual dose is 1.0 mg/ mL of DNase in 2.5 mL of excipient once daily. DNase must be refrigerated (2–8°)	• Traditional jet nebulisers (e.g. Pari LC jet nebuliser or equivalent), intelligent nebulisers (I-neb/ eFlow devices) are smaller, quicker devices that give improved deposition of medications and reduce inhalation time to less than 5 min • Tidal breathing interspersed with larger inspiratory volumes to optimise deposition • DNase should delivered through a different chamber than other medications (such as antibiotics)	• Rare but can include conjunctivitis, dysphonia, dyspnoea, pharyngitis, laryngitis, rhinitis (all noninfectious), dyspepsia; rash, urticaria; chest pain (pleuritic/noncardiac), pyrexia, pulmonary function tests decreased

Mucoactive	Drug response assessment (DRA)	Timing with ACT/other medications	Dose	Delivery device/ breathing pattern	Side effects
Mannitol	Mannitol specific DRA	• Airway clearance should be commenced 15 min after inhalation of mannitol	• 400 mg twice daily (10 × 40 g capsules via inhaler BD). Time is critical to maintain the osmotic gradient. Prolonged intervals between doses should be avoided	• Osmo-inhaler. The patient should tilt their head back slightly, lips tight around the inhaler, and perform controlled slow deep inhalation (60 L/min) and hold breath for 5 s. The capsule should rattle during inhalation. Remove the inhaler from mouth and exhale, resuming normal breathing. Check capsule after each inhalation. If capsule is not emptied, a second immediate inhalation may be required	• Dry throat or cough. But this is expected • Bronchospasm can occur. If a hyperresponsive reaction is suspected during treatment, mannitol should be discontinued. Review patients at 5 weeks of treatment to assess for bronchospasm • Other reported rare side effects have included: nasopharyngitis, cough, lower respiratory tract infection, headache, haemoptysis, dyspnoea, back pain, sinusitis, diarrhoea, nausea
		• The patient should use a bronchodilator 15 min prior to inhalation of mannitol			
Bronchodilators	Yes (looking for positive response)	• 15 min prior to ACT	• Dependant on specific drug	• Dependant on specific drug	

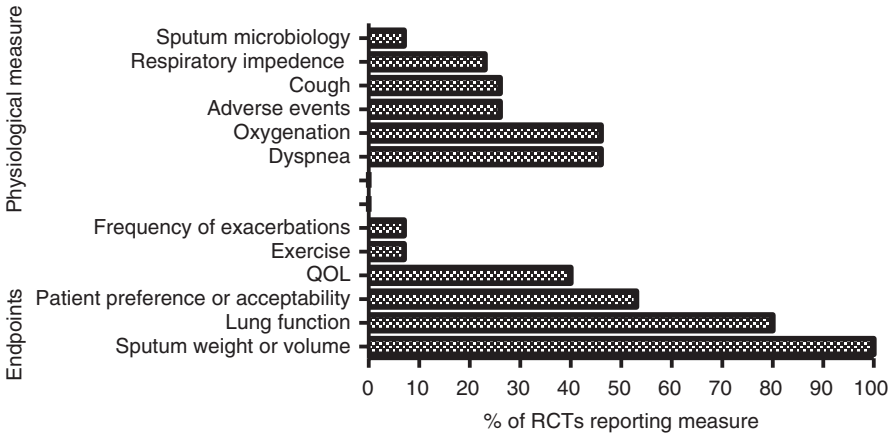

Fig. 18.1 RCT's of ACT in bronchiectasis (n = 15): percentage reporting each type of outcome measure

bronchiectasis guidelines [65] British Thoracic Society (BTS) and BTS/Association of Chartered Society of Physiotherapists in Respiratory Care (ACPRC) guidelines. Marques and colleagues highlighted the limitations of more conventional endpoints such as Forced Expiratory Volume in 1 s (FEV_1) and urged consideration of new emerging outcome measures whilst considering patient preference factors [66].

To highlight the lack of consensus on endpoints for ACT trials, we have summarised the outcome measures used in 15 RCTs of ACT in bronchiectasis [27, 29, 34, 38–47, 67] of which 7 were included in the Cochrane review [68] (Fig. 18.1). Measures used include both endpoints (clinical or surrogate) and physiological measurements and each has associated strengths and weaknesses (Table 18.4). Physiological measurements (i.e. oxygenation, dyspnoea, respiratory impedance) are useful to gain understanding of the mechanism of an ACT and should be chosen based on the aims of treatment and in combination with a clinically meaningful endpoint [66, 69, 70]. Whilst this data gives some direction on which groupings of endpoints to focus on, there still remains a need for consensus on a set of core outcomes to use for ACT trials, to facilitate key comparisons between studies.

In addition to these clinical and surrogate endpoints, there are a number of patient related factors that are crucial to the outcome of an ACT intervention. These include patient knowledge and proficiency with the technique, patient satisfaction and adherence, patient confidence with performance and adherence to the technique and any patient barriers to performing the ACT. It is important to measure these aspects both in practice and in trials of ACT. It has been recently highlighted that patient preference can heavily influence the success of a study as has been demonstrated in a number of CF clinical trials (Sontag, Pryor), where dropouts lead to failure to adequately recruit. This highlights the need to consider patient preference early in study planning and design as well as to consider different study designs for example Rucker design [69].

Table 18.4 Commonly reported endpoints in RCTs of ACT in bronchiectasis: strengths and weaknesses

Outcome measure	Strengths and weaknesses
Clinical endpoints (i.e. reflect how a patient feels, functions or survives)	
Pulmonary exacerbation	+ Relevant to patient
	+ Little associated cost
	+ Standardised definition
	+ Frequent pulmonary exacerbation, are a predictor of lung function decline [71]
	+ Can be dependent on self-report as pulmonary exacerbation, can be managed in primary or secondary care
	+ Further consideration required for situations involving home antibiotic treatment and oral antibiotics
HRQoL	+ Relevant to patient [17, 72, 73]
	+ Widely available with little associated cost
	+ Standardised in the form of validated questionnaires
	+ SGRQ independently associated with mortality
	+ QOL B bronchiectasis specific questionnaire
	+ Norm values available
	– Ceiling effect in mild disease with questionnaires
	– Dependent on self-report
Surrogate endpoints(i.e. used to predict the efficacy of therapy when direct measurement of clinical effect is not feasible or practical)	
Expectorated sputum	+ Relevant to patient [17]
	+ Widely available with little associated cost
	– Difficult to standardise and quantify
	– Some patients do not expectorate
	– Unclear what size of improvement or direction of change (i.e. increase or decrease) corresponds with clinically meaningful improvement
	– Poor reliability and validity
Lung function	+ Relevant to the patient
	+ Widely available
	+ Standardised
	+ Spirometry, total lung capacity (TLC) &TLC/reserve volume (RV) independently associated with mortality [72, 74]
	+ Norm values available and data on norm rate of annual decline
	– Spirometry insensitive in early or mild disease
	– Body plethysmography technically demanding to carry out
	– Requires large number of patients to show a statistical
	– Significant difference

18.7.1 Pulmonary Exacerbations

The presence of three or more pulmonary exacerbations annually is independently predictive of mortality [19]. Pulmonary exacerbation, in bronchiectasis, is defined as the requirement for antibiotics in the presence of one or more symptoms of increasing cough, increasing sputum volume, worsening sputum purulence, worsening dyspnoea, increased fatigue/malaise, fever and haemoptysis [16, 17].

Only one study of ACT in bronchiectasis to date has included pulmonary exacerbation, as an endpoint reporting no significant difference in the number of

pulmonary exacerbation, in 20 patients over 12 weeks [34]. Researchers performing trials in ACT should use an established exacerbation definition to facilitate both comparison and meta-analysis of data across trials and consider different of aspects of exacerbation including frequency, duration of or incidence of hospitalisation or total number of hospitalised days.

18.7.2 Health Related Quality of Life

HRQoL assessment is obtained directly from the patient and assesses how they feel or function with respect to their health condition. Chronic cough, expectoration of sputum and breathlessness can affect how an individual functions and socialises. As ACTs aim to facilitate the clearance of sputum and reduce associated symptoms and potential impact on daily living, this effect can be evaluated.

A range of questionnaires are applicable to use in bronchiectasis patients including the St. George's Respiratory Questionnaire (SGRQ), the Quality of Life-Bronchiectasis (QOL-B), Leicester Cough Questionnaire (LCQ) and Short Form-36. All offer a validated measure with good psychometric properties and measure aspects of health not captured by objective measures [75]. The SGRQ is the most widely studied questionnaire, whilst the QOL-B is the only questionnaire developed specifically for bronchiectasis [75]. Both have demonstrated responsiveness with inhaled therapies in bronchiectasis [73, 76].

To date, 3 RCTs from the Cochrane review of ACT in bronchiectasis have incorporated a QOL measure [34, 42]. A significant change, equivalent or greater than the minimum important difference, in LCQ and SGRQ score has been shown with treatment consisting of HFCWO, a mix of ACT and oscillatory PEP compared to no treatment.

18.7.3 Measures of Expectorated Sputum

Expectorated sputum amount, measured either by volume or wet weight is often used as an outcome but can be confounded by unintentional expectoration of saliva with the sample and/or swallowing the sputum. The interpretation in longer-term studies can be challenging as an increase in sputum expectorated over time could indicate that treatment is being effective due to improved clearance or ineffective because the underlying infection in the lung is increasing. Conversely, a decrease in sputum expectorated could indicate that treatment is less effective, or that the underlying infection is resolving. Evaluation of expectorated sputum is subject to interpretation.

Bacterial load of sputum can also be assessed, although if the mucus load is reduced by an effective ACT, it may become difficult to assess accurately. The bacterial density in sputum can also be measured but is also confounded by sampling issues. If a particular ACT works by dislodging long-impacted sputum, which is known to become a nidus for infection, the intervention may be associated with

an increased in bacterial density, even if it decreases the overall bacterial load in the lungs.

Two of the RCTs in bronchiectasis studies reported significant increases in the mean volume of wet weight sputum expectorated with oscillatory devices in the short- and long-term highlighting that it can demonstrate responsiveness [34, 39].

18.7.4 Pulmonary Function Tests

Whilst FEV_1 may be an important safety measure in airway clearance trials, its relevance and suitability as an outcome is debatable. It is well established that FEV_1 is insufficiently sensitive to detect changes in the peripheral airways and annual rate of change in lung function in bronchiectasis is small [66, 69, 77–80]. Furthermore, measures of spirometry (% predicted) are heavily influenced by the choice of reference ranges which can be variable across studies [81]. FEV_1 has been used as an outcome for many ACT trials in bronchiectasis (Fig. 18.1); however the Cochrane review concluded that the effect of ACT on lung function in the studies reviewed was variable [68]. Of the six studies to evaluate pulmonary function, only one reported a statistically significant difference in the treatment group compared to control [42].

18.7.5 Body Plethysmography

Other pulmonary function outcome measures chosen as endpoints in ACT trials in bronchiectasis include functional residual capacity (FRC), TLC and RV measured using body plethysmography. High RV/TLC ratios and lower TLC have been shown to be independently predictive of mortality, highlighting the importance of obstruction in the presence of restriction in bronchiectasis [72, 74]. Two RCT of ACT in bronchiectasis studies reporting on FRC and TLC reported a significant reduction in pulmonary hyperinflation with non-PEP ACT compared to no ACT [40, 42]. The mechanism behind these effects may vary depending on the chosen ACT, for example, PEP may splint the airways preventing dynamic airway collapse, whilst oscillating techniques may target specific lung volumes associated with hyperinflation [68]. This emphasises that future studies of ACT in bronchiectasis should be evaluated considering the known pathophysiology.

18.7.5.1 Exercise

Exercise capacity was measured as a secondary outcome in only 1 RCT of ACT in bronchiectasis. Murray and colleagues demonstrated a significant improvement in the distance walked by patients (using the incremental shuttle walk test) after 3 months of twice daily oscillatory PEP compared to no physiotherapy. Whilst field walking tests such as the shuttle walk test/modified shuttle test have good clinimetric properties in respiratory population, improved exercise tolerance is a longer-term goal of ACT and therefore more relevant as an endpoint in longer-term ACT trials.

18.7.6 Novel Endpoints

Novel endpoints to study the effect of ACT optimise the chances of detecting physiological changes that have not yet been demonstrated or identified. Small cohort studies represent the first steps to understanding which measures could hold potential. Adoption of novel endpoints into larger scale studies depends primarily on responsiveness, as well as feasibility and affordability.

18.7.6.1 Ventilation Distribution Indices

In respiratory disease, changes in the peripheral airways results in ventilation inhomogeneity (VI) [82]. The study of LCI in bronchiectasis is less developed than in other respiratory conditions, but to date has shown good clinimetric properties as an outcome measure and superior sensitivity compared to FEV_1 [18, 83]. The responsiveness of LCI with ACT is less clear. One study assessed the short-term responsiveness of LCI with ACT in bronchiectasis during stability and pulmonary exacerbation and found no measurable impact [84]. It is proposed that this variability may be because ACT opens up previously "blocked off" areas caused by mucus plugging, or relieve areas of atelectasis, opening up a poorly ventilated areas, thereby causing a rise (worsening) in LCI. This highlights a potential limitation of LCI as an outcome measure for ACT, as there is potential for a bidirectional response to therapy.

18.7.6.2 Imaging

In a cohort study by Svenningsen and colleagues, magnetic resonance imaging (MRI) was used to measure change in ventilation post 3 weeks of ACT (oscillatory PEP) in 15 bronchiectasis patients [85]. They reported an improvement in ventilation greater than the minimum clinically important difference in half of the patients. These studies highlight that MRI could offer a new way to objectively evaluate response to ACT therapy. Although this is currently not a routinely available lung imaging modality.

In conclusion is recognised as a core component of the overall management of bronchiectasis and has been highlighted as a priority area for research by both patients and clinicians. Important research questions include establishing long-term effectiveness of ACT, how ACT and mucoactive drugs should be combined to optimise MCC, as well as how ACT can be personalised to subgroups of patients. Future trials that use novel designs and important clinical endpoints, as well as long-term observational data from large datasets such as EMBARC, will potentially support a more personalised approach to ACT in bronchiectasis and contribute to the current evidence base.

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Pulmonary Rehabilitation in Bronchiectasis

19

Annemarie L. Lee and Anne E. Holland

19.1 Introduction

Pulmonary rehabilitation is a comprehensive and multi-faceted approach to the management of the patient with lung disease. The American Thoracic Society and European Respiratory Society defines pulmonary rehabilitation as "a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies that include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and psychological condition of people with chronic respiratory disease and to promote the long-term adherence to health-enhancing behaviours" [1]. Consistent with international best practice guidelines, the primary objectives of a rehabilitation programme for people with bronchiectasis are to alleviate the physiological effects, reducing the psychological impact of this condition, and maximise compliance to changes in health behaviour [2].

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Much of the evidence base for pulmonary rehabilitation has been derived from studies focused on individuals with chronic obstructive pulmonary disease (COPD), for whom rehabilitation is part of the standard of care [3]. However, the similarities in symptoms and physiological effects in individuals with bronchiectasis compared to COPD lend conceptual support for this intervention in bronchiectasis [4], a position further encouraged by recommendations that pulmonary rehabilitation programmes accept and enrol patients with bronchiectasis [2]. Emerging data indicate the efficacy of pulmonary rehabilitation for improving patient-centred outcomes such as functional exercise capacity, symptoms and health-related quality of life [5], all key outcomes that align with international recommendations for pulmonary rehabilitation [2].

Although the scope of research of pulmonary rehabilitation in bronchiectasis is lagging behind that of COPD, surveys of clinical practice indicate that physiotherapists do refer patients to this intervention [6, 7], with a mix of models of rehabilitation examined in recent years. This chapter will review the literature outlining the clinical rationale for pulmonary rehabilitation, characteristics of those who are suitable, type of rehabilitation which have been applied and their clinical effects, options for assessing outcomes and, finally, the future challenges of pulmonary rehabilitation for this population.

19.2 Physiological Rationale

Common clinical symptoms of bronchiectasis are sputum production, dyspnoea and fatigue [8, 9]. The causes of dyspnoea are multifactorial, but key factors include altered respiratory mechanics and impaired gas exchange. While the majority of individuals present with an obstructive pulmonary defect, a mixed obstructive/restrictive defect is not uncommon [10, 11], secondary to fibrotic and emphysematous changes consistent with chronic inflammation. Expiratory airflow limitation has been identified in those with moderate to severe bronchiectasis, with an increase in dynamic hyperinflation and heightened levels of dyspnoea [12, 13]. Together with respiratory muscle weakness [14] and lower quadriceps strength and endurance, this has been linked to reduced exercise tolerance [12, 13], with a lower 6-min walk distance (6MWD) reported in those with bronchiectasis compared to age-matched healthy controls [13]. Reduction in the 6-min walk test (6MWT) corresponds with findings from incremental symptom-limited exercise testing in people with bilateral bronchiectasis [15], which demonstrated that a proportion of individuals have reduced maximal power and oxygen uptake, with lower maximal ventilation and breathing reserve at peak exercise [15]. Expiratory flow limitation was a predictor of reduced maximal exercise capacity and corresponded to higher levels of dyspnoea [15].

Higher levels of fatigue (present in 74% of people) [8, 9] are experienced by individuals with bronchiectasis, and this symptom is associated with increased dyspnoea [13], as well as greater depression and anxiety [16–18]. This combination of peripheral and respiratory muscle impairment, symptoms of dyspnoea and

psychological consequences contribute to poorer health-related quality of life (HRQOL) [19, 20]. Collectively, these clinical features of bronchiectasis, which are similar to COPD [3] support the rationale for pulmonary rehabilitation for improving exercise capacity and HRQOL [2].

19.3 Who Are Suitable Participants?

The selection criteria of individuals with bronchiectasis who have been enrolled in studies of pulmonary rehabilitation are outlined on Table 19.1. To date, in terms of disease severity, no specific restrictions have been imposed, with FEV_1% predicted ranging from 46% to 77% predicted [21–23] or individuals classed with mild to severe obstruction based on spirometry. Benefit has been reported in those with varicose or cylindrical bronchiectasis with either singular or double lung involvement [14, 23, 24]. While it is not yet clear whether disease severity influences the clinical effect of pulmonary rehabilitation, the lack of adverse events in pulmonary rehabilitation trials across the disease spectrum indicates the safety of this intervention. In addition, according to pre-lung transplantation guidelines, pulmonary rehabilitation is advocated for those with very severe bronchiectasis awaiting lung transplantation [25]. While little information is available related to the underlying cause of bronchiectasis or associated colonisation, those with idiopathic disease, childhood- or adult-onset infections and immunodeficiency disorders have been included in clinical trials [14, 21, 23, 24], with a history of exacerbations not uncommon [21, 26]. Although not yet applied in studies of pulmonary rehabilitation, measures of severity using the Bronchiectasis Severity Index or the FACED score (FEV_1, age, colonisation, radiological extension and dyspnoea) [27, 28] may

Table 19.1 Physiological and clinical features of people with bronchiectasis undertaking pulmonary rehabilitation in clinical trials

	Range of mean values
Physiological features	
FEV_1% pd	45–76% (77)
FVC % pd	79–84%
Clinical features	
6MWD (m)	443–578 m
ISWD (m)	286–474 m
Degree of dyspnoea (MMRC score)	≥1
Total SGRQ score[a] (points)	38.6–91
Total CRDQ score[b] (points per item)	12.7–13.9
Total LCQ score[c] (points)	12.3–14.5

[a]Total score ranges from 0 to 100, higher score indicates better quality of life
[b]Total score ranges from 0 to 28 points per item, higher score indicates better quality of life
[c]Total score ranges from 3 to 21, higher score indicates better quality of life
FEV_1 forced expiratory volume in 1 s, *% pd* percent predicted, *FVC* forced vital capacity, 6MWD 6-min walk distance, *ISWD* incremental shuttle walk distance, *MMRC* modified Medical Research Council dyspnoea score, ≥ greater than or equal to 1, *SGRQ* St George's Respiratory Questionnaire, *CRDQ* Chronic Respiratory Disease Questionnaire, *LCQ* Leicester Cough Questionnaire

provide further guidance in the future. While most commonly applied when clinically stable, the significant improvement in exercise capacity and HRQOL in patients with COPD who undertake pulmonary rehabilitation post-acute exacerbation [29] suggests that those with bronchiectasis in a similar clinical state may also be suitable for enrolment. In addition, despite limited information, undertaking pulmonary rehabilitation during an acute exacerbation of bronchiectasis was not associated with adverse events [30]. The baseline level of functional exercise capacity of pulmonary rehabilitation participants has ranged from a 6MWD of 443–578 m to an incremental shuttle walk distance (ISWD) of 286–474 m [21, 24] (Table 19.1). While disease-specific HRQOL may vary from severe to mild impairment, these parameters align with recommendations for referral and enrolment of people with bronchiectasis who demonstrate functional limitations [2].

19.4 Assessment Tools

Patient-centred outcomes are central to assessing the effectiveness of pulmonary rehabilitation in chronic respiratory disease. With the strongest evidence emerging from measures of exercise capacity, symptoms and HRQOL, these outcomes form the minimum of assessment criteria for this intervention. For some tools, a minimal clinical important difference (MCID) has been defined. The MCID is defined as the smallest difference in a measurable clinical parameter that indicates a meaningful change in the condition for better or for worse, as perceived by the patient or clinician [31]. While often derived from a group response, many MCID estimates provide criteria for assessing change in an individual. Measurements should be completed before and at the conclusion of pulmonary rehabilitation to assess effectiveness.

19.4.1 Exercise Capacity

Exercise training is a core component of pulmonary rehabilitation, and thus change in exercise capacity is an important outcome. Exercise performance can be assessed using field walking tests or laboratory tests such as incremental treadmill tests or cycle ergometry. The most common tools used to assess functional exercise capacity in bronchiectasis are the incremental shuttle walk test (ISWT) and the 6MWT. The ISWT uses external pacing to assess exercise capacity and is classed as a symptom-limited maximal exercise test, with the distance walked strongly associated to peak aerobic capacity [32]. Conversely, the 6MWT is a self-paced test. Both tests are applied using standardised instructions [33] to maximise external validity. In chronic respiratory diseases, reliability and validity for both tests has been well established [32]. Specific to bronchiectasis, the 6MWT and ISWT have demonstrated strong reliability, although the presence of a learning effect indicates the need to follow a protocol of completing two tests at the commencement and conclusion of pulmonary rehabilitation in order to accurately determine the clinical effect of this intervention [34]. The MCID for the 6MWT has been described in people with

bronchiectasis as 22–25 m and for the ISWT as 35–37 m (four shuttles) [35], both consistent with previous reports in chronic respiratory populations for these outcome measures [32, 36]. While both tests are responsive to training, the ISWT is marginally more sensitive to measures of change [34], possibly due to the external pacing of the test. Although little used, the endurance shuttle walk test (ESWT) has demonstrated evidence of change following rehabilitation in bronchiectasis [24] and is the most responsive field walking test for assessing the clinical effect of pulmonary rehabilitation in COPD [37]. The decision of which field walking test to apply will depend on test properties and practical considerations. The potential ceiling effect of the 6MWT in individuals with better preserved lung capacity [32] supports the use of the ISWT as a more optimal choice. While the ESWT may be the most responsive test, it is a more time-consuming measurement.

Laboratory-based exercise measures such as symptom-limited incremental or constant-rate cardiopulmonary exercise tests (CPET) provide thorough information relating to cardiovascular and respiratory parameters at both submaximal and maximal exercise workloads. This includes measures of peak work rate, cardiorespiratory function variables, including peak heart rate, respiratory rate, peak oxygen consumption (VO_2), carbon dioxide output (VCO_2), minute ventilation and measures of dyspnoea and fatigue [38]. Despite the complexity of testing, laboratory tests are responsive to exercise training and have been applied in bronchiectasis [14]. The advantage of their application over a field walking test is the greater detail regarding the degree of ventilatory or cardiovascular limitation to exercise capacity [38]. For patients with bronchiectasis who have concurrent cardiovascular disorders, a CPET may be more useful in identifying the physiological contributions to exercise limitations compared to a field walking test and provide more detailed and accurate information to guide the prescription of exercise intensity (e.g. as a percentage of peak work or peak VO_2). From a practical perspective, their selection for use is largely dependent on access to facilities and equipment, time and cost considerations and the alignment of the test with the exercise training procedure. For instance, cycle-based testing protocols are more likely to be sensitive to change following pulmonary rehabilitation programmes that include a large cycle training component and less likely to be sensitive to change following walking programmes.

19.4.2 Quality of Life

Changes in HRQOL following pulmonary rehabilitation can be evaluated with either generic or disease-specific tools, with clinical practice and research studies indicating that disease-specific tools are predominantly used in this population. The St George's Respiratory Questionnaire (SGRQ) and Chronic Respiratory Disease Questionnaire are valid and reliable in bronchiectasis [19, 39] and have demonstrated responsiveness to change following pulmonary rehabilitation [24]. Evaluation of cough-related quality of life is relevant in bronchiectasis, with the Leicester Cough Questionnaire a valid and reliable tool [40, 41] which has been applied as a

patient-reported outcome measure following rehabilitation [21, 24]. Although not established in people with bronchiectasis, the MCID is reported as 4 points for the total SGRQ score, 0.5 points per domain for the CRDQ and 0.2 (physical), 0.2 (social), 0.8 (psychological) per domain and 1.3 for the total LCQ [42–44]. The majority of pulmonary rehabilitation studies have applied the SGRQ as the most common HRQOL tool.

More recently, the Quality of life-Bronchiectasis tool has been developed which provides a measure of symptoms, function and quality of life [45, 46]. With established reliability and validity in patients with bronchiectasis, the MCID for respiratory symptoms is 8 points [46]. Although yet to be used in evaluating pulmonary rehabilitation, the comprehensiveness of this measure may provide a more thorough HRQOL evaluation to previously applied tools. Its availability in 30 languages has considerable practical application.

19.5 Additional Assessments

The COPD Assessment Test (CAT), while originally designed to assess health status in individuals with COPD, has demonstrated evidence of validity in bronchiectasis [47]. It is an additional option for assessing well-being following rehabilitation in bronchiectasis, its benefits being the minimal time required for completion and ease of scoring, while its disadvantages are related to limited detail provided regarding health status.

With fatigue and dyspnoea being key features of bronchiectasis, assessing for change in these symptoms following rehabilitation is an additional option in clinical practice. A variety of contextual and intensity measures are available, such as the Multidimensional Fatigue Inventory, Pulmonary Functional Status and Dyspnoea Questionnaire (modified version), the Multidimensional Dyspnoea Profile and the Baseline Dyspnoea Index [48–51]. Depression is also common in bronchiectasis, so review of the effect of pulmonary rehabilitation using the Hospital Anxiety and Depression Scale or Beck's Depression Inventory [52, 53] is an appropriate option. Although these tools are yet to be validated in bronchiectasis and have not been used in trials of pulmonary rehabilitation in this population, studies of rehabilitation in COPD have indicated their responsiveness [1, 54].

The analysis of data in real time for assessment tools maximises the opportunity to provide timely feedback to patients regarding potential improvements in symptoms, exercise levels and HRQOL at the conclusion of a programme, which may be important clinical motivators encouraging ongoing exercise training and physical activity beyond the supervised sessions.

19.5.1 Physical Activity in Bronchiectasis

Physical activity is increasingly important in chronic respiratory disease, particularly due to the relationship between regular physical activity and prognosis [55].

Physical activity in daily life is described as "the totality of voluntary movement produced by skeletal muscles during everyday functioning" [56]. Sedentary behaviour has been identified in individuals with bronchiectasis; out of 55 patients, only 11% met the criteria for physical activity guidelines [57]. Those who undertook moderate intensity physical activity in greater than 10 min sessions had higher levels of social functioning [57]. Severity of disease impacted on physical activity; those with moderate or severe disease spent less time in daily total moderate and vigorous physical activity and had lower activity energy expenditure compared to those with mild disease. This sedentary behaviour in bronchiectasis may be influenced by psychological factors, such as low levels of confidence in specific situations (i.e. when experiencing respiratory symptoms) which may impact upon their ability to participate. A larger proportion of patients have been identified to be in the pre-contemplation or contemplation phase of behavioural change, which was reflected by their lower levels of physical activity compared to those in the action and maintenance phase of behavioural change [57]. There is a need for greater social support in those with lower physical activity levels [58].

Multiple questionnaire-based and objective measures of physical activity are available and may be applied in people with bronchiectasis undergoing pulmonary rehabilitation. Although the effects of pulmonary rehabilitation on physical activity in bronchiectasis is yet to be explored, evidence of physical activity changes following this intervention in other chronic respiratory conditions is disappointing. A systematic review in COPD demonstrated that supervised exercise training incurred only a small benefit in physical activity [59]. With reduced physical activity being a clinical feature of bronchiectasis, strategies to address this within pulmonary rehabilitation are necessary. A focus on incorporating approaches which facilitate behavioural change may be required to achieve clinical benefits.

19.6 Models of Rehabilitation

19.6.1 Exercise

Exercise training is most commonly applied in an outpatient setting for individuals with bronchiectasis who are in a stable clinical state. The duration of training usually ranges from 8 to 12 weeks [14, 21, 23, 24, 60], consistent with current recommendations for pulmonary rehabilitation in COPD [1]. Generally, programmes incorporate a minimum of two or three sessions of supervised training per week. Home training is considered important for the longevity of training effects, with the individual directing their own programme [21] or following an established routine [24], with a degree of external support [30]. Models of inpatient rehabilitation have also been applied for those with bronchiectasis [26, 30, 60]. The duration of programmes are typically shorter, varying from 5 days to 4 weeks, with some patients admitted in a stable clinical state [26, 60] and others commencing training while experiencing an acute exacerbation of bronchiectasis [30]. Characteristics of training programmes used in clinical trials are in Table 19.2.

Table 19.2 Type of training for inpatient and outpatient exercise programmes reported in clinical trials

	Endurance exercise	Duration and frequency	Intensity	Strength exercise	Duration and frequency	Intensity	Outcome measures	Findings
Outpatient programmes								
Mandal 2012	Treadmill	10 min/equipment	85% of VO_2 max	UL and LL exercises	NR	60% of 1RM, 3 × 10	ESWT, ISWT	Improvement in ISWD by 56.7 m and ESWT by 193.3 m; both > MCID
	Bike Ski machine					Progression to 70% and 80%	LCQ, SGRQ	Improvement in LCQ by 2.6 points and in SGRQ by 8 points; both > MCID
Newall 2005	Treadmill	45 min in total	80% peak HR on maximal incremental exercise test	NI	NR	NR	Endurance exercise capacity	No difference in VO_2 peak
	Cycle ergometry							Improvement in endurance exercise capacity with exercise (392.8 m)
							ISWT	Improvement in ISWD 96.7 m; >MCID)
	Stair climbing						SGRQ	No difference in SGRQ

Ferreira 2006	Treadmill Recumbent bicycle Recumbent stepper Stair climbing Cycle ergometer	NR	NR	Upper limb ergometer Free weights	NR	NR	6MWT CRDQ	Specific results not reported for bronchiectasis
Ong 2011	Treadmill Cycling	30 mins in total	Treadmill: 70% of baseline 6MWT speed, progressed 0.25–0.5 km/h weekly Cycling: Borg SOB 3–4	Upper limb free weights Lower limb functional activities	NR	NR	6MWT CRDQ	Improvement in 6MWD 53.4 m Change in dyspnoea (4.8 points), fatigue (3.2 points), emotional function (3.7 points), mastery (2.3 points), all > MCID
Van Zellar 2012	Cycling	30 min	Target load of 60% max work rate	Upper limb Quadriceps	NR	NR	6MWT	Improvement in 6MWD by 25 m

(continued)

Table 19.2 (continued)

	Endurance exercise	Duration and frequency	Intensity	Strength exercise	Duration and frequency	Intensity	Outcome measures	Findings
Lee 2014	Treadmill	15 min each exercise	Walking: 75% of ISWT	Upper limb free weights	Approximately 20 min	Aimed for Borg scale 3–4, RPE 12–14	ISWT, 6MWT	Improvement in ISWD by 62 m and 6MWT by 41 m; >MCID
				Lower limb functional activity with weights				Less dyspnoea and fatigue but no change in emotional function or mastery
	Stationary cycling		Cycling: 60% of peak work, derived from 6MWD				CRDQ, HADS, LCQ	No change in anxiety, depression or LCQ scores
Inpatient programmes								
Foster 1990	Treadmill	Total of 45 min	Within patient's tolerance	Upper limb resistance training	NR	Within patient's tolerance and improvement in activities of daily living	6MWT	Improvement by 91 m; >MCID)
	Ground-based walking							
	Stationary cycling							

Zanini 2014	Treadmill	30–40 min	60–70% of maximal HR of 6MWT	Upper limb calisthenics or arm ergometer	NR	NR	6MWT	Improvement in 6MWD by 35 m; >MCID
	Cycle ergometry						EQ-VAS BDI	Less dyspnoea (change ≥1 unit in BDI and EQ-VAS improvement by 15 points
Greening 2014	Ground-based walking	Daily	Speed set at 85% oxygen consumption from incremental shuttle walk test	Biceps, triceps, knee extension, sit to stand, step ups	NR	1RM 3 sets of 8 repetitions	ISWT, ESWT SGRQ	No difference in ESWT, ISWD and SGRQ total score at discharge or 6wks, 3 months or 12 months

min minutes, VO_2 maximal oxygen consumption, *UL* upper limb, *LL* lower limb, *IRM* one-repetition maximum, *HR* heart rate, *SOB* shortness of breath, *6MWT* 6-min walk test, *6MWD* 6-min walk distance, *ISWT* incremental shuttle walk test, *ESWT* endurance shuttle walk test, *MCID* minimal clinically important difference, VO_2 peak oxygen consumption, *LCQ* Leicester Cough Questionnaire, *SGRQ* St George's Respiratory Questionnaire, *CRDQ* Chronic Respiratory Disease Questionnaire, *HADS* Hospital Anxiety and Depression Scale, *EQ-VAS* European Quality-Visual Analogue Scale, *BDI* Baseline Dyspnoea Index, *NR* not reported, *NI* not included

19.7 Exercise Prescription

Within the model of pulmonary rehabilitation, exercise training is a cornerstone feature. Common options for the setting of group-based exercise are either in an outpatient hospital department or within a community health or rehabilitation centre, where supervision is provided. The goal of endurance training in bronchiectasis is to achieve skeletal muscle adaptation and minimise the effects of deconditioning, an approach adapted from the principles of training those with COPD [1]. Studies based their exercise prescription on data obtained from maximal or functional exercise testing at baseline [14, 21, 23, 24, 61]. Generally, the workload in those who are clinically stable is of a moderate intensity at 60–70% maximal workload (Table 19.2), predominantly using cycling and walking (Fig. 19.1). For inpatient rehabilitation, the clinical status of the patient is likely to direct the intensity of exercise prescription, with variable options applied between studies (Table 19.2). Those who are stable had used a similar exercise prescription intensity as outpatient programmes [26]. In contrast, the intensity setting for those with an exacerbation of bronchiectasis is more variable, ranging from a daily walking speed set at 85% of oxygen consumption estimated from the endurance shuttle walk test or a manageable speed for those unable to achieve a speed of 1.8 km/h [30]. Less clear is the method of progression for endurance exercise; approaches using symptoms of dyspnoea and fatigue and the discretion of an experienced physiotherapist have been applied [21, 26, 30].

The other key feature of exercise programmes is resistance training. This focuses on the activation of local muscle groups in repetitive lifting exercises, generally using a moderate intensity load [62], with both upper and lower limb muscles targeted. The options for resistance training are functional exercise (i.e. sit to stand and step ups, using body weight to provide resistance) or free weight exercises (using

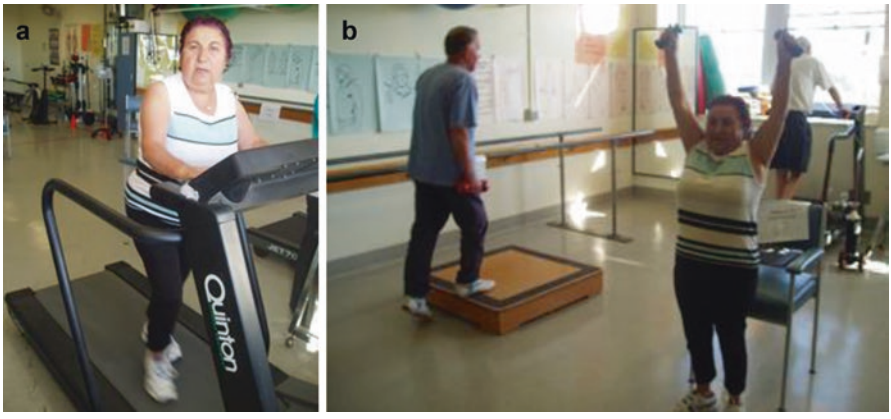

Fig. 19.1 Patients exercising during pulmonary rehabilitation. (**a**) Endurance exercise on a treadmill, (**b**) lower and upper limb resistance exercise. (Permission to publish images has been granted by individuals)

dumbbells) (Fig. 19.1). In bronchiectasis, a mix of these exercises has generally been included [21, 23, 24, 30, 61, 63], with the use of one-repetition maximum to set training loads reported [24, 30].

Not all individuals with bronchiectasis may require group-based training. For those who have less time availability and demonstrate sufficient motivation towards an individual routine, prescribing an exercise programme to be completed in a private or public gym may be a suitable alternative. This may be more appealing to a younger population, in whom the number of comorbidities may be less compared to older individuals and are able to safely undertake an unsupervised exercise programme. For selected individuals who are sufficiently motivated and engaged in physical activity interventions, the provision of exercise advice regarding intensity and frequency, accompanied by suggestions for modes of exercise is a clinically suitable approach.

19.8 Education

Education and self-management form a fundamental part of pulmonary rehabilitation for individuals with COPD [1] and has been recognised as an important feature of overall treatment for patients with bronchiectasis [64]. Within inpatient and outpatient pulmonary rehabilitation programmes, a mix of topics can be incorporated into education sessions. These have ranged from self-management, airway clearance techniques, the role of adherence to therapy, nutritional support, disease pathology, rationale for ongoing home exercise training, relaxation, medication, coping strategies and inhaler techniques to psychosocial support [14, 22–24, 26, 30, 61]. Like exercise training, the inclusion of these topics is largely derived from what has been applied for COPD. Although it is currently not known whether these topics are the optimal choice for education and self-management for bronchiectasis, or whether they are meeting patients' needs, it is important that disease-specific education is the focus of an education programme. If accompanied by a practical session on airway clearance techniques or correct use of inhalers, this provides scope for enhanced education and learning for individual patients. The format may range from a formal lecture series to a self-management manual, with the optimal approach for this population not understood.

19.9 Outcomes of Pulmonary Rehabilitation

19.9.1 Short-Term Effects

The clinical effects of pulmonary rehabilitation have been examined in a mix of retrospective and prospective studies, using maximal exercise and field walking tests in addition to clinical questionnaires (Table 19.2). For changes in functional exercise capacity according to field walking tests, the degree of improvement in the 6MWD has varied from 25 m to up to 53 m [21, 23, 26, 60, 63], which is within the

clinically significant range for patients with chronic respiratory diseases [32]. Of the three randomised controlled trials, the degree of improvement in ISWD ranges from 57 m to 92 m [14, 21, 24], also beyond the MCID for this outcome [36]. Statistically significant improvements in measures of endurance walking capacity have also been noted in differing models of pulmonary rehabilitation (Table 19.2) [14, 24]. Despite differences in programme intensity and duration between studies, the magnitude of effect on exercise capacity does not appear to differ between an inpatient or outpatient programme.

Both exercise training alone and exercise and education achieved clinically significant improvements in HRQOL [21, 24]. In contrast, the improvement in cough-related QOL may depend on the type of rehabilitation programme; exercise, education and an airway clearance regimen result in benefit [24], while exercise alone had no effect [21]. Less dyspnoea has been noted during inpatient and outpatient programmes [21, 26], matched with less fatigue.

The contribution of education to the overall effects of pulmonary rehabilitation is unclear. While comparison is limited with seven studies including education as well as exercise and only one study examining exercise training alone, the magnitude of change in functional exercise capacity and HRQOL is similar across studies. Therefore, the clinical effects of education require further evaluation.

19.9.2 Long-Term Effects

The longevity of the effects of pulmonary rehabilitation is not well documented, with follow-up periods in clinical trials ranging from 3 to 12 months. Benefits were still noted 3 months after programme completion in clinical trials [14, 24]. A retrospective study also found sustained improvement in exercise capacity above the baseline levels at 3 months, although declines at 6 and 12 months post programme were evident [63]. In contrast, a prospective clinical trial of exercise training alone observed an inability to maintain these improvements over the same time frame [21]. In patients with COPD, some studies have shown longer-term improvements with maintenance programmes [65], although this is not consistently demonstrated [66]. Although the optimal model of maintenance is not known, this approach could be considered for individuals with bronchiectasis undertaking pulmonary rehabilitation in order to sustain benefit.

19.10 Acute Exacerbations and Time to First Exacerbation

With acute exacerbations of bronchiectasis influencing morbidity [67], reducing the frequency has broad clinical implications. Only one clinical trial has examined the effect of outpatient-based exercise training on these outcomes, with fewer exacerbations over 12 months and a longer time to first exacerbation compared to those not undertaking exercise training [21]. However, the precise mechanism of this improvement is not clear, with the impact on functional exercise capacity and HRQOL not

sustained over the same time frame, a similar observation to that demonstrated in COPD [68]. A programme commenced during an acute exacerbation with the same length of follow-up was not associated with fewer hospitalisations [30].

19.11 Comparisons to Other Disease Groups (COPD)

Pulmonary rehabilitation results in well-documented and clinically important improvements in patient-centred outcomes for patients with COPD, and thus a comparison against this benchmark is warranted. In a study where responses to pulmonary rehabilitation in individuals with bronchiectasis were directly compared to individuals with COPD undertaking the same programme (exercise and education), the degree of improvement for functional exercise capacity and HRQOL did not differ between groups [63]. In contrast, Whidden et al. [69] demonstrated a larger degree of change in the 6MWD in favour of bronchiectasis (52 m compared to 19 m for COPD), and similar responses were evident for HRQOL. Achieving equivalent if not better outcomes compared to those with other respiratory conditions, such as COPD who have a long-standing inclusion in pulmonary rehabilitation, lends further support to the inclusion of patients with bronchiectasis.

19.12 Adjuncts to Pulmonary Rehabilitation

Some individuals with bronchiectasis may benefit from adjunctive therapies in pulmonary rehabilitation, in addition to exercise training and education. The rationale for these additional therapies is largely based on other physiological features of bronchiectasis, including respiratory muscle weakness and sputum expectoration.

19.12.1 Inspiratory Muscle Training

With respiratory muscle weakness identified in those with bronchiectasis, inspiratory muscle training has been used as an adjunct to a pulmonary rehabilitation programme [14]. In addition to endurance training for 8 weeks, one group also completed inspiratory muscle training (IMT), commencing at 30% and increasing to 60% PImax, twice daily [14]. Benefits in inspiratory muscle strength and HRQOL were achieved only in those undertaking the IMT; however, improvements in whole body exercise capacity were evident regardless of this training. Some lasting effects in endurance capacity of those undertaking IMT were present 3 months after completion of pulmonary rehabilitation [14]. These findings are consistent with home-based IMT alone for a period of 8 weeks, commencing at the same intensity and progressing by 2 cm H_20 weekly, for up to 30 min/day [70]. No greater improvement in 6MWD or HRQOL was achieved in those performing the training compared to those who did not. Despite the greater longevity of improvement after 3 months of completing rehabilitation [14], IMT is not traditionally part of

pulmonary rehabilitation and greater clarification of its role in this population and its potential for carry-over effects is necessary.

19.12.2 Neuromuscular Electrical Stimulation

Neuromuscular electrical stimulation is a form of non-volitional training that can be applied regardless of the individual's ability to mobilise or exercise. For patients with bronchiectasis, this has included neuromuscular training applied to bilateral quadriceps, 15 s on, 5 s off, which was commenced during the inpatient and outpatient programme for those with an acute exacerbation [30]. While it is considered a possible training modality for those with severe COPD, its benefits for those with well-preserved exercise capacity is unclear [1] and its effect on quadriceps strength in those with bronchiectasis was minimal [30].

19.12.3 Airway Clearance Techniques

Individuals with bronchiectasis are frequently prescribed airway clearance techniques (ACTs) as part of their daily treatment routine [71, 72]. However, the significance of ACTS as part of pulmonary rehabilitation is not clear. A weekly check of a pre-set airway clearance routine offered little advantage, with no change in cough-related QOL compared to those not receiving a check [21]. Instruction in ACT as part of the education has been applied [24, 60], but additional benefits were not apparent. For individuals who note that exercise enhances their ability to expectorate secretions, guidance in use of the forced expiratory technique during an exercise programme may be beneficial [73].

19.13 Future Direction for Pulmonary Rehabilitation in Bronchiectasis

Greater clarity is required regarding when pulmonary rehabilitation should be commenced for patients with bronchiectasis. This is a clinical challenge, with some individuals diagnosed with bronchiectasis as children and others diagnosed at adults, by which time symptoms may have been present for several years. Exercise options will differ between children and adults in order to be age-appropriate. With the varying causes of bronchiectasis, it is unclear whether the clinical effects of pulmonary rehabilitation are influenced by the aetiology. Additional information on functional outcomes, such as the sit to stand and gait speed tests and measures of physical activity, will provide further indications as to the longevity of clinical effects of PR in this population and the generalisability to daily life. In addition, examining the adjunct effects of airway clearance therapy within a rehabilitation routine and how this may be prescribed to optimise pulmonary rehabilitation outcomes is unclear. With education sessions largely based on what is provided for

individuals with COPD, identifying appropriate, patient-selected education topics for bronchiectasis is of clinical value. Effective self-management is considered critical for patients with bronchiectasis; the incorporation of this within a pulmonary rehabilitation programme and its impact on clinical outcomes remain to be explored.

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Surgical Treatment and Lung Transplantation in Bronchiectasis

20

Dragan Subotic and Jessica Rademacher

20.1 Rationale for Surgical Treatment

The rationale behind surgical treatment of localized form of disease is to break the *circulus vitiosus* starting from bronchiectasis, through consecutive inflammation and toxin release with impaired mucociliary clearance, to subsequent destruction as a final consequence. Apart from interrupting this harmful course, operation removes the segments that are no longer functional, in the same time preventing the infectious contamination of adjacent lung zones and leading to significant symptom relief.

The key points for successful outcome of surgical treatment are (1) complete resection of all diseased lung zones, poorly penetrated by antibiotics, thus serving as a reservoir of bacteria; (2) optimal timing of the operation in order to avoid a loss of time, development of drug resistance, and spread to adjacent lung segments; (3) pre- and postoperative antibiotic therapy based on sensitivity testing; and (4) pre- and postoperative physiotherapy [1].

20.2 Indications for Surgery

Some patients with localized disease may fail optimal medical treatment or become resistant to such a treatment. In this situation, disease progression is associated with persistent symptoms that negatively affect their quality of life and especially their working capacity [2–4]. Although this is the most frequently cited reason for

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referring patients to surgery, many patients with complications of bronchiectasis, requiring urgent or elective surgery, will remain outside such a frame. This relates primarily to patients with massive hemoptysis or pleural empyema requiring surgery. Furthermore, in certain percentage of highly symptomatic patients with similar type and distribution of the lesions, the decision for the operation is not only based on the overall physician's assessment, but on subjective interpretation of the existing discomfort in the private and professional life by the patient as well. It may influence to some extent the sizes of the published surgical series, but certainly not the reported distribution of indications for surgical treatment, as presented in Table 20.1.

In all published surgical series, the most frequent indication for the operation was recurrent infections with productive cough and fetid sputum, followed by repeated or massive hemoptysis. Other indications were less frequent. The mean

Table 20.1 Indications for the operation (%)

	Recurrent infections	Hemoptysis	Abscess	Undiagnosed lung mass	Pnth	Empyema	Without symptoms	Symptom duration
Fujimoto [14] (n 92)	62.2	23.3[a]	10	3.3	0	1.1	0	10.6 (0–50) years
Balkanli [41] (n 238)	68.4	16.4	0	1.7	0	0	4.2	2.4 (1–18) years
Kutlay [42] (n 166)	95.2	3	1.8	0	0	0	0	5.7 years
Prieto [15] (n 119)	55	26.5	9	8	3	0	0	4 (1–40) years
Agasthian [43] (n 134)	63.4	19.4	9	8.2	0	0	9.7	6 (1–60) years
Eren [44]	74.1	14.6	6.2	NR	0	4.8	2	28.5 (0–156) months
Zhang [38]	100		NR	NR	0	0	0	36 (2–360) months
Hiramatsu [5]	42	29	NR	NR	0	0	6	68 (3–248) months
Caylak [45]	67.8	–	–	–	–	–	6.2	39.3 (1–216) months
Al Rafaelle [46]	71.7	15.9	8	4.3	0	0	0	9 (3.70 ± 2.3) years
Balci [47]	56.9	12.8	NR	5.3	0	0	0	43.4 ± 36.9 months
Valillo [39]	100	57.4[c]	NR	NR	NR	NR	0	NR[d]
Al Kattan [13]	73	35[b]	NR	NR	NR	NR	0	3.4 ± 2.9 (1–19) years

[a]Total percentage of pts. with hemoptysis in the series, including 4 pts with massive hemoptysis
[b]Total percentage of hemoptysis, not a main indications for surgery
[c]Not a primary indication for surgery
[d]More than 1 year of medical treatment or frequent exacerbations

symptom duration was in the range 1.45–14.9 years. Most of the evidence about symptom duration comes from developing countries—27 studies, compared with 11 studies coming from developed countries. In fact, only three studies came from developed countries after 2001 [5–7].

20.3 Diagnostics

20.3.1 Imaging

Standard chest radiography may sometimes be strongly suggestive of bronchiectasis, although it is usually not a case. More frequently, subsequently confirmed bronchiectasis has the aspect of undetermined, poorly defined lung masses (Fig. 20.1).

In the presence of typical symptoms, associated with unclear, or even normal appearance on PA radiography, a lateral radiography or CT should be done, because the lesions may be localized behind the heart and thus overlooked (Fig. 20.2).

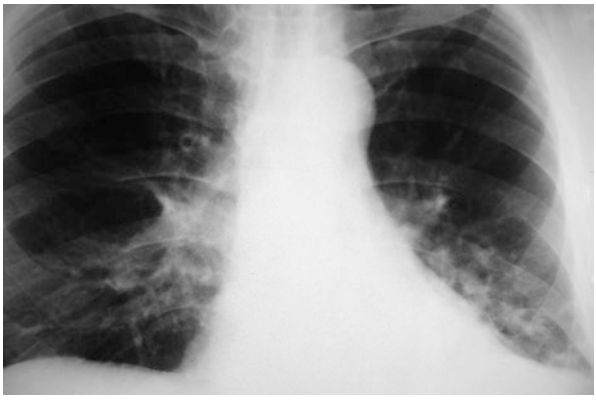

Fig. 20.1 Frequent radiographic aspect of bronchiectasis—poorly defined lung mass in the left lung

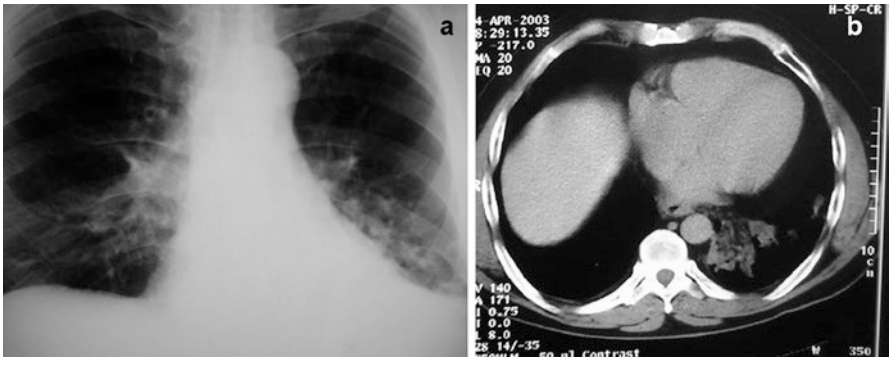

Fig. 20.2 Lesion is localized behind the heart—diagnosis is obtained by CT

After mid-1990s of the twentieth century, high-resolution computed tomography (HRCT) has replaced contrast bronchography, which has been considered for many decades as the gold standard for diagnosis of bronchiectasis. Modern software, with only 2% false-negative and 1% false-positive rates, provides a detailed insight into morphology and distribution of the lesions that is essential for planning surgical treatment [8–10]. Apart from typical aspect of cystic/saccular or cylindrical dilatations of the bronchi (Fig. 20.3a), the existence of the internal diameter of the affected bronchus that is greater than the accompanying bronchial artery and a lack of bronchial tapering may be highly suggestive of bronchiectasis [11]. In addition, a so-called "tram track" sign may exist in some patients as well (Fig. 20.3b).

However, it is sometimes really difficult to distinguish CT aspect of bronchiectasis on CT from other diseases, like malignancy or chronic or atypical pneumonia, irrespective of symptoms (Fig. 20.4). That is why the percentage of bronchiectasis diagnosed after surgery for undiagnosed lung masses remains stable throughout the literature even with the use of high-resolution CT, as presented in Table 20.1.

Apart from the expected correlation between the extent of disease on HRCT scans and quality of life and lung function, the localization of the lesions itself may be of some clinical importance. Bilateral bronchiectasis in the middle lobe and

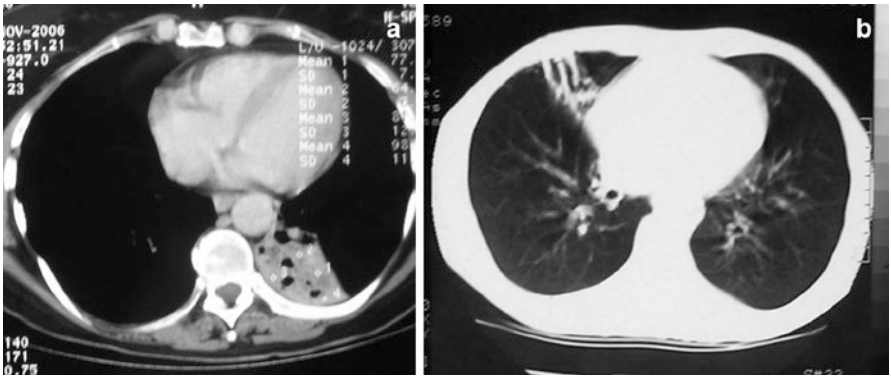

Fig. 20.3 CT aspect of bronchiectasis (**a**) typical aspect; (**b**) "tram track" sign

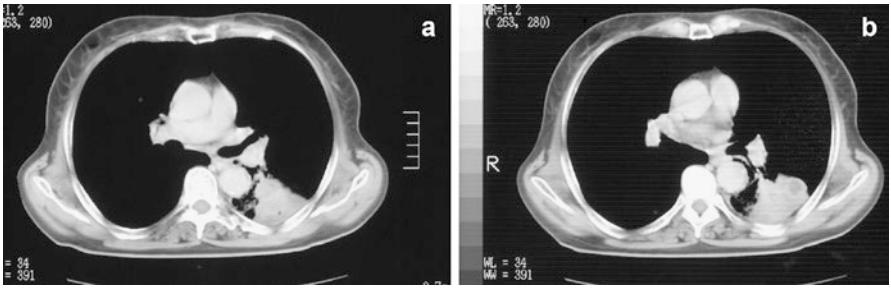

Fig. 20.4 Tumorlike appearance of bronchiectasis

lingula should raise suspicion to nontuberculous mycobacterial infection. The upper lobe involvement may be suggestive of cystic fibrosis (CF), while proximally located bronchiectasis represents one of the main features of aspergillosis [12].

20.3.2 Perfusion Pattern Analysis

The perfusion pattern of bronchiectasis is well established long ago and may be of interest for preoperative selection. Basically, bronchiectasis may be perfused or non-perfused. Cylindrical type of bronchiectasis is usually associated with the retained perfusion, while cystic bronchiectasis is usually non-perfused (Fig. 20.5). Based on these findings, some authors advocated the attitude to avoid surgery for well-perfused bronchiectasis, offering it only for non-perfused type, with the explanation that perfused bronchiectasis still retains the ability of the gas exchange [13].

However, such an attitude is not widely accepted for two reasons: firstly, in some series with many patients with cylindrical bronchiectasis, medically resistant symptoms existed and were successfully alleviated by surgery in 1/3 of patients [14]; secondly, in many patients with bronchiectasis, lung function is not a major issue, being quite well preserved, like in the series on 119 patients with a postoperative FEV_1 drop from 83% before to 81% after surgery [15]. It was also demonstrated that the main lung function remains well preserved even after resection of one or two bronchiectatic lung lobes [16, 17].

The reason for such a pattern of postoperative lung function change may be the smaller lung volume of the lobe with bronchiectasis compared with the non-affected lobe, as presented in Fig. 20.6.

Possible explanation of rare findings of significantly lower late postoperative FEV_1 compared to preoperative values could be the fact that, for example, in one series, a "more important" drop of FEV_1 related to postoperative FEV_1 drop >15%, which existed in only 9/35 (25.7%) patients, while in 11/35 patients with contralateral disease foci, more than nonfunctional parenchyma had to be removed for anatomical reasons.

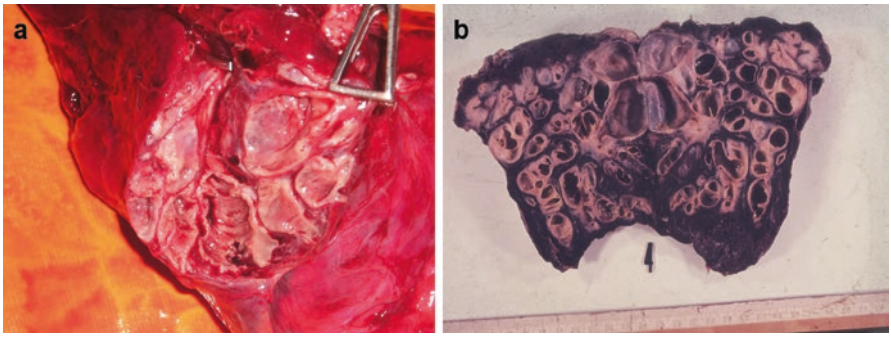

Fig. 20.5 Cystic (non-perfused) bronchiectasis localized in one lobe (**a**) and involving the entire lung (**b**)

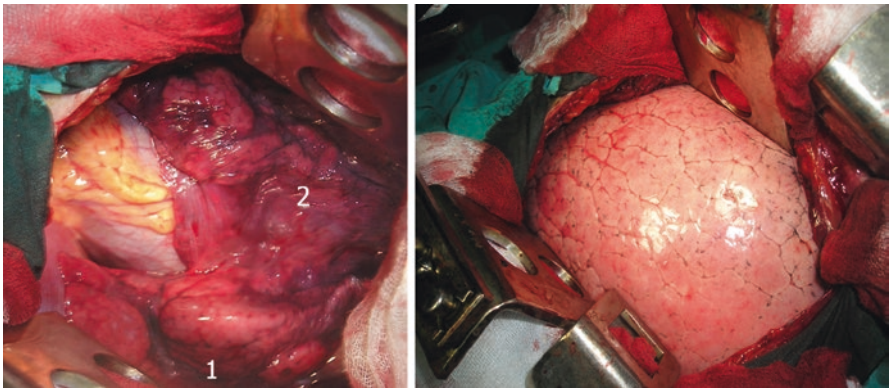

Fig. 20.6 Difference in the lobe size in a patient with bronchiectasis—operative view left thoracotomy for bronchiectasis; left 1: lower lobe affected by bronchiectasis; 2: non-affected upper lobe; right: reexpanded upper lobe after the lower lobectomy

Recently, two studies have demonstrated a decrease in FEV_1 of approximately 50 mL/year in patients with bronchiectasis [18]. It was also reported that *P. aeruginosa* infection accelerated a decline in lung function and caused more frequent exacerbations [19]. Therefore, surgery should be considered while the disease is still localized and without signs of *P. aeruginosa* infection. That can result in preserving as much lung function as possible and, consequently, achieve a better long-term surgical outcome.

Regardless of the influence to preoperative selection, data obtained from earlier angiographic studies helped to understand the significance of the anastomotic blood flow between pulmonary and bronchial circulation in these patients. This is because a retrograde anastomotic flow from the bronchial arterial system, opposite to the direction of flow from the pulmonary artery, may be dominant, in a way to prevent the contrast medium in the pulmonary artery to reach the lung periphery during pneumoangiography, giving the aspect of the absent perfusion from the pulmonary artery (Fig. 20.7). In case of localized bronchiectasis, no major hemodynamic consequences will ensue, but, in the presence of more diffuse distribution of bronchiectasis, the drainage of that flow through the bronchial veins may cause the left heart embarrassment. The described dominant retrograde stream within major pulmonary arteries, in case of diffuse distribution, may cause the right heart embarrassment as well.

An example of a better preserved perfusion is presented in Fig. 20.8.

Of course, pneumoangiography is not more used in the preoperative selection. The perfusion\ventilation (V/Q) lung scan is noninvasive and can be easily combined with HRCT scan. It was also suggested that perfusion scintigraphy might be equivalent or even superior to ventilation scintigraphy in predicting postoperative lung function [20]. In case that non-perfused regions on perfusion scans correspond to HRCT findings, the non-perfused lung zones will be targeted by surgery. If the scans show a good perfusion, bronchiectatic territories in accordance with the

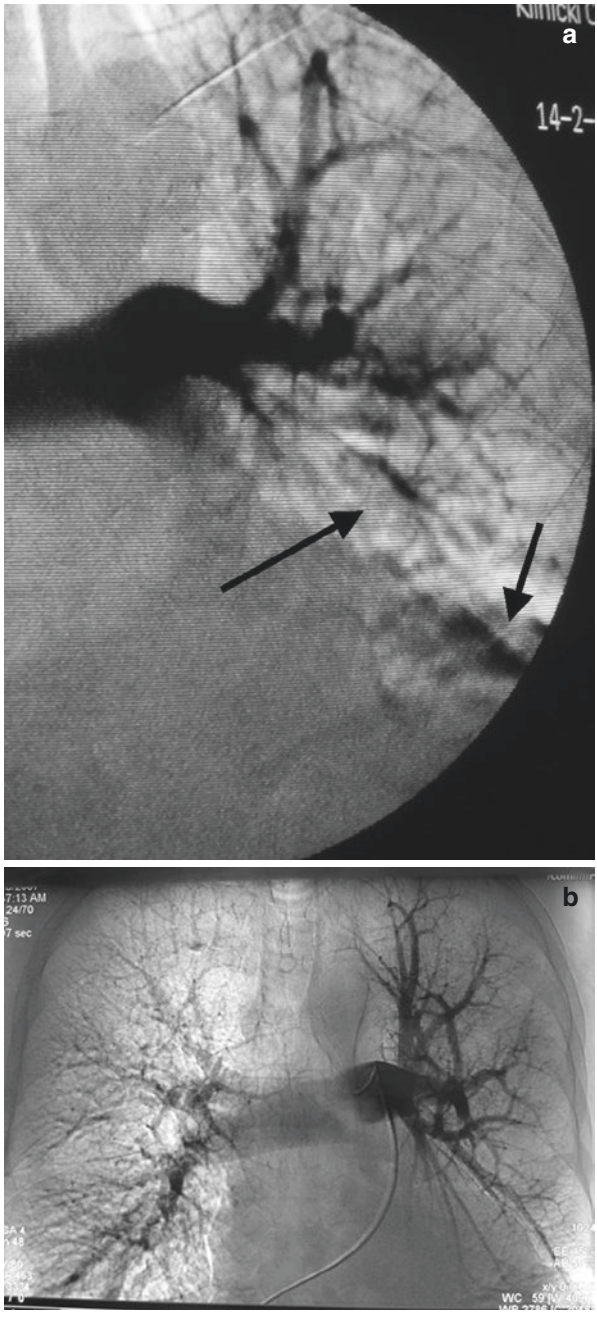

Fig. 20.7 Perfusion pattern (**a**) *long arrow*: region of absent perfusion; *short arrow*: retrograde flow from bronchial circulation (**b**) poor perfusion in the lower lobe

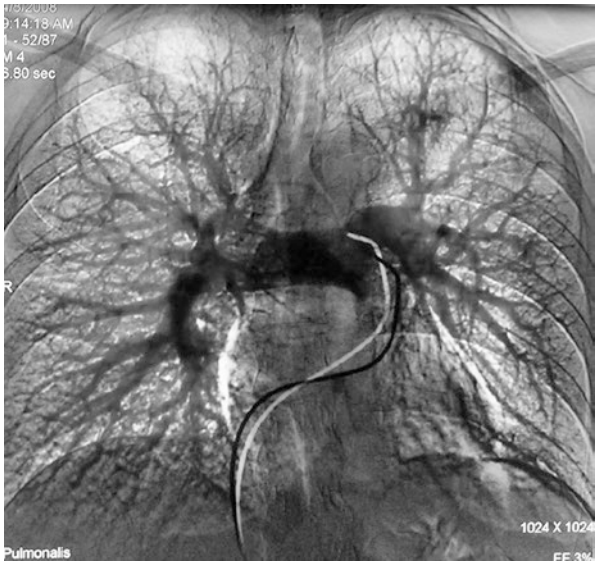

Fig. 20.8 Bronchiectasis in the left lower lobe with well-preserved perfusion

HRCT findings, non-perfused territories of the lungs were primarily targeted for resection in the preoperative planning. When the scans showed good perfusion, the rationale for continuation of medical treatment is the assumption that the blood stream has a direct access to bronchiectatic zones enabling healing by medical treatment. As mentioned, such an approach is not widely accepted and reported.

20.3.3 Bronchoscopy

Bronchoscopy is mandatory in all candidates for surgical treatment. The goal of bronchoscopy is threefold: (1) to identify causative microorganisms, (2) to rule out endobronchial pathology, and (3) to assess the severity of infection. The latter is particularly important and should be done on the day of surgery, even if previously done for other two reasons. If on day of surgery signs of moderate or severe endobronchial infection exist, operation should be postponed until full control of infection.

20.4 Preparation for Surgery and Extent of the Lung Resection

The key rule of surgical treatment is to avoid operating in the presence of infection. Operation should be postponed at least until a resolution of endobronchial signs of the infection is achieved as assessed by bronchoscopy, which usually takes an additional week of treatment or even more. Bronchial aspirate and sputum should be routinely cultured. Culture-positive patients should undergo a specific antibiotic therapy until they became culture-negative. In other patients, prophylactic antibiotics for 48 h

Table 20.2 Extent of resection (%)

	<Lobect	Lobect	Bilobect	Pneumo	Lob + seg
Fujimoto (n 92)	33.7	54.3	5.4	6.5	
Balkanli (n 238)	2.1	79.4	–	5.46	–
Kutlay (n 166)	12.2	69.8		7.5	10.5
Prieto (n 119)	13	62	3	8	14
Agasthian (n 134)	13.4	64.2	–	15.7	6.7
Eren (n 143)	29.2	55.4	4.7	8.3	2.7
Zhang (n 790)	4.7	62.9	7.1	11.3	14
Hiramatsu (n 31)	6/33	19/33	2/33	1/33	5/33
Al Rafaelle (n 138)	2.2	81.2	8.7	8	–
Balci (n 86)	24.8	38.8	9.7	19.4	6.4
Valillo (n 53)	0	83	0	17	0

before surgery should be given. All patients should be subjected to the intensive preoperative physiotherapy, including postural drainage for at least 2 weeks. In case of significant sputum production, physiotherapy and antibiotic treatment should be continued until the daily sputum volume is diminished or eliminated. According to the literature, lobectomy is the most frequently performed operation, either alone or combined with ipsilateral sublobar resection if a part of the adjacent lobe is affected as well (Table 20.2). Segmental resection is justified whenever possible in order to spare the lung parenchyma. Anatomical lingular resection is a frequent choice. Preservation of the VI segment is sometimes possible in patients with basal segmentectomy and may not be associated with increased morbidity, as previously reported [21, 22]. In patients with the destroyed lung, pneumonectomy is the only option.

20.5 Major Clinical Problems

20.5.1 Bilateral Bronchiectasis

In patients with bilateral bronchiectasis, traditionally, the most frequent concerns for treating physicians were: (1) whether to operate at all? (2) What are the alternatives? (3) If resection is to be done, which side should be operated first? (4) Are the primary criteria for resection symptom-based only or symptom-based combined with angiography?

Currently, it is clear that bilateral disease itself is not always a contraindication for resection, but in these patients, prolonged conservative treatment and bronchial artery embolization are frequently used as alternatives. Furthermore, the percentage of incomplete resection is clearly higher if more than lobe is involved. It was also demonstrated that it is possible to achieve similar outcome in patients with bronchiectasis affecting at least one segment in two different lobes, either unilaterally or bilaterally [23].

In published surgical series, the percentage of bilateral bronchiectasis varied between 5.8% and 30%, in the majority of them being under 20%. Although the percentage of patients with bilateral disease who underwent a bilateral thoracotomy varied between 5.8% and 100%, the absolute number of patients with bilateral operation in individual series rarely exceeded 10. There is still no consensus as to whether the more

or less affected side should be operated first, because this point is not sufficiently evidence-based. The attitudes vary throughout the literature from still dominant approach that the more severely affected side should be operated first, through acceptance to operate first the less affected side, to simultaneous or staged bilateral thoracotomy [24].

Related to selection criteria, suggestions that, in case of bilateral disease, only non-perfused bronchiectasis should be operated are not widely accepted. As already mentioned in the section about perfusion pattern, in 1/3 of operated patients in one series cylindrical (perfused) bronchiectasis existed, but associated with medically resistant symptoms, that were successfully alleviated by the operation [14]. On the other hand, in the series of Al Kattan [13], by strictly applying selection based on the perfusion pattern, all patients with mixed bilateral localized cystic and scattered cylindric (perfused) bronchiectasis had symptom improvement with low morbidity after resection of the localized cystic areas.

To summarize, in patients with bilateral bronchiectasis, it may seem reasonable to take the perfusion pattern into account when deciding which side to operate first or whether to do bilateral operation at all, if contralateral disease foci have a preserved perfusion.

20.6 Hemoptysis

As presented in Table 20.1, hemoptysis occurs in a quite high percentage of patients with bronchiectasis, but it is difficult to precisely determine the proportion of patients in whom hemoptysis represent the main indication for surgery, because of inconsistency in reporting these data throughout the literature. Hemoptysis is mild in the majority of patients and frequently the first symptom to lead the patient to consult a physician. Massive hemoptysis, originating from dilated bronchial arteries, is rarely lethal [25–27]. However, they have been reported in a quite high proportion of patients with a decreasing trend from 51% in a report from South Africa [28], through 20% in a report from New York [29], to 20% in a report from Israel [30]. Even in the presence of hemoptysis, radiographic aspect may not be suggestive of bronchiectasis, like in a series of 67 patients, with some unclear opacities in 54%, but typical enough to establish the diagnosis in only 19% of them [31].

Surgery is certainly the procedure of choice for massive hemoptysis, but emergency surgery in unstable patients is associated with higher morbidity and mortality reaching 37% [32]. In that case, embolization of the bronchial arteries should be done whenever possible, although it is only a temporary solution aimed to postpone surgery until the patient's general condition improves and the bleeding site is identified.

20.7 Bronchiectasis Causing Lung Abscess

In this group of patients, bronchoscopy is of utmost importance in order to rule out the lung cancer. It was demonstrated that in patients with a pulmonary abscess, bronchoscopy, combined with sputum cytology, may reach a high diagnostic yield, correctly identifying patients with underlying malignancy in up to 88% patients

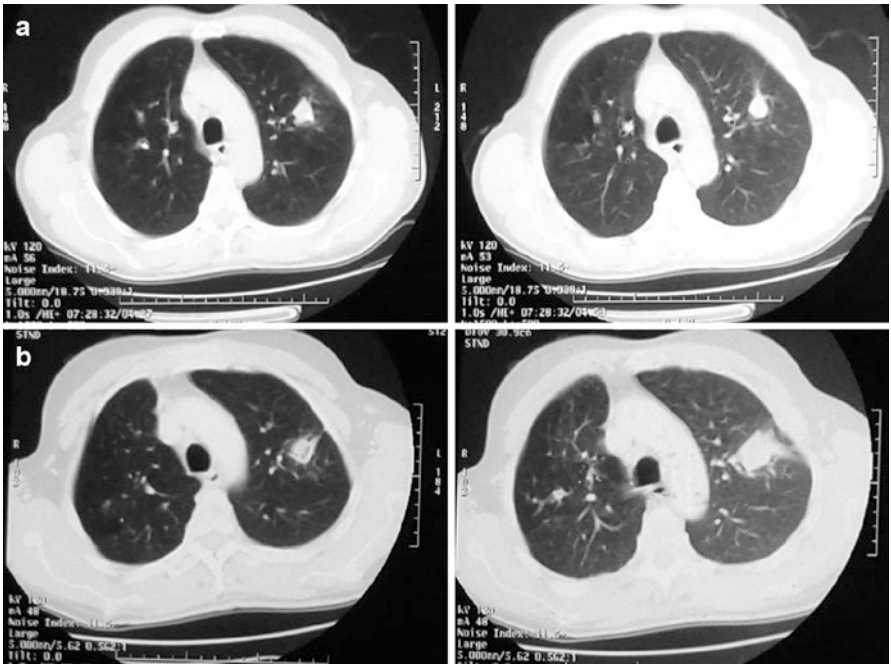

Fig. 20.9 Bronchiectasis with lung abscess with a CT aspect suggestive of malignancy

[33]. Similar results were confirmed by some other case reports, demonstrating that in patients with pulmonary abscesses resistant to antibiotics, the definitive diagnosis of malignancy may not be possible prior to surgery, despite appropriate noninvasive and invasive diagnostics [34]. An example of localized bronchiectasis with lung abscess with a CT aspect suggestive of malignancy is presented in Fig. 20.9.

In addition to the usual clinical course with repeated respiratory infections in the presence of typical radiographic aspect, there are some specific situations, sometimes representing a real clinical challenge. One of this exists if the operation is planned for persistent, undetermined lung masses, after previously treated pleural empyema, as presented in Fig. 20.10. In this situation, apart from the need to rule out lung cancer intraoperatively, the possibility of bronchiectasis and lung abscess should also be kept in mind. In the presented patient, bronchiectasis was confirmed on the resected specimen. As can be seen in Fig. 20.10b, macroscopic aspect may be very similar both to lung cancer and organizing pneumonia. Furthermore, due to necrosis, frozen section during the operation may not be absolutely reliable, making the decision about the extent of resection more difficult. In the presence of important interlobar, perivascular, and peribronchial fibrosis, great care should be taken to avoid resection greater than necessary.

If the disease course is not typical for bronchiectasis, especially in the presence of mild hemoptysis, irregular cavitary lung lesions (Fig. 20.11), and a bronchoscopic aspect that is not suggestive of lung cancer, bronchiectasis should be also considered. In the presented patient, it was not until the definitive pathological report when bronchiectasis was confirmed on the operative specimen.

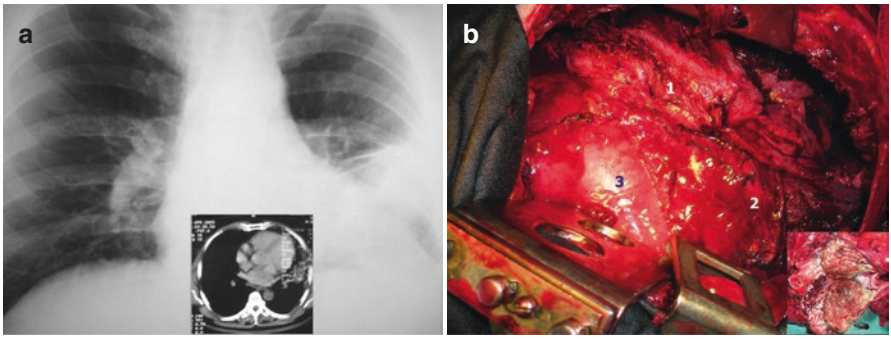

Fig. 20.10 Surgery for bronchiectasis after pleural empyema (**a**) preoperative aspect; (**b**) operative view: *1*: thickened parietal pleura overlying the left upper lobe; *2*: lower lobe; *3*: diaphragm; insert: cross-sectional aspect of the intralobar tumorlike mass subsequently diagnosed as bronchiectasis

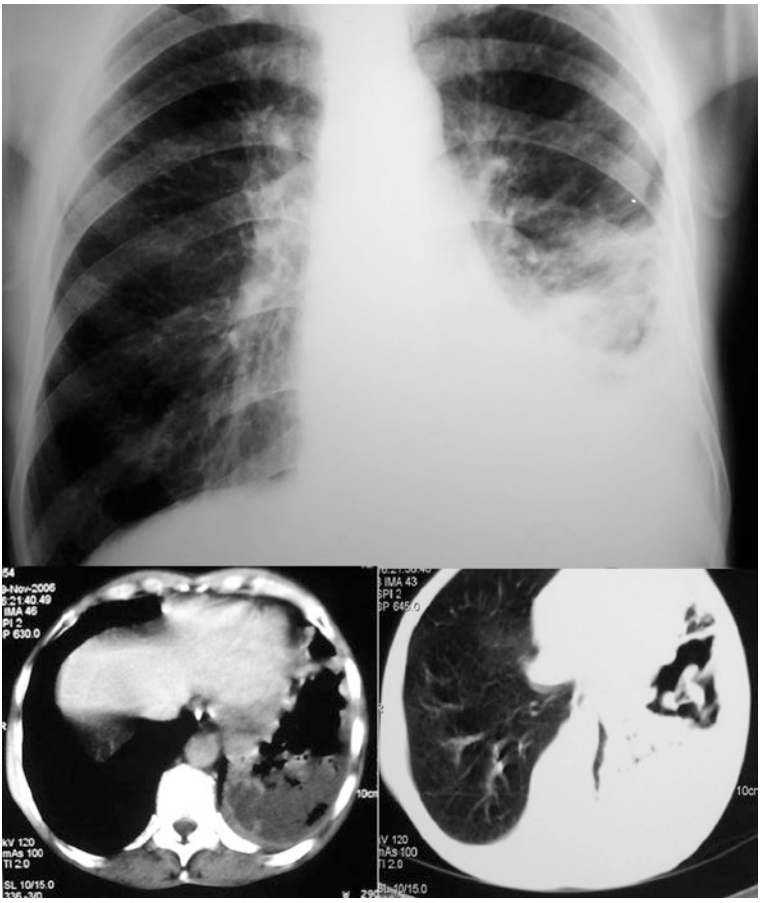

Fig. 20.11 Bronchiectasis: unclear lung densities and cavitation

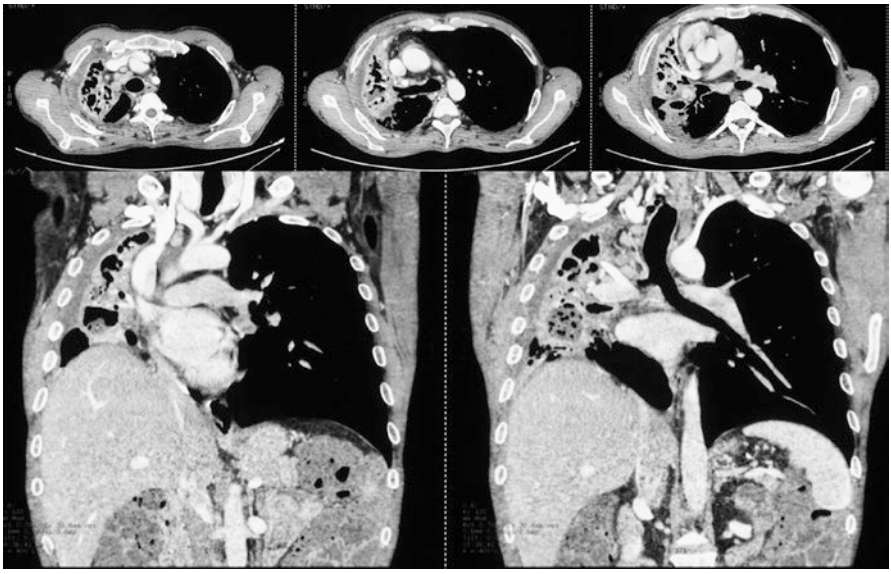

Fig. 20.12 Bronchiectasis: destroyed lung (pleuropneumonectomy)

20.8 Destroyed Lung

This is a clear indication for straightforward surgery, especially in symptomatic patients. It may be indicated as the initial operation or as a redo-surgery after previous lung resection for bronchiectasis. In a series with 23 patients with a completion pneumonectomy, recurrent infections as the indication for surgery existed in 15/23 patients, with 4.9 years mean interval between the operations, zero operative mortality and 43.5% 30-days operative morbidity [35]. The lung destroyed by bronchiectasis may also be the cause of pulmonary hypertension, even with healthy contralateral lung [36]. It is sometimes possible to do a pneumonectomy without a major extrapleural dissection. However, in many patients extensive extrapleural dissection is necessary, together with intrapericardial approach to the lung vessels. Care should be taken to avoid spillage of secretion from the lung cavities, because fetid and highly virulent infection may exist within the lung, even in the absence of clinical signs of infection (Fig. 20.12).

20.9 Role of VATS in Surgical Treatment of Bronchiectasis

With the increasing use of VATS surgery in general, there is also some space for its use in patients with bronchiectasis, especially in those with bilateral disease, where bilateral staged sublobar resections are anticipated. The rationale for its use in older patients is better preservation of the lung function, while in younger patients, a better cosmetic result is dominant.

In patients with a bilateral disease, candidates for VATS, quantitative perfusion scintigraphy (CPECT-CT) may be useful in patients with limited lung function [37]. Whether it is appropriate to do VATS resections earlier in the disease course, even without marked symptoms, in order to prevent the disease spread to other lung zones and subsequent major resections, is not sufficiently evidence-based.

In case of bilateral, well-localized disease, a single-stage bilateral VATS procedure is also an option, superior to two-stage bilateral open procedure. Rare studies comparing the efficiency of VATS vs. open surgery for bronchiectasis found the two procedures comparable in relation to symptomatic improvement (94% vs. 88%), but with shorter hospital stay and less complications (17.5% vs 23.7%) and pain after VATS procedures [38]. Prerequisites for VATS surgery in patients with bronchiectasis are (1) experienced centers with a high volume of VATS procedures, (2) no major parenchymal or pleural scarring, and (3) no calcified nodes close to the hilar lung vessels [24].

20.10 Treatment Outcome

In a meta-analysis of 35 articles with 4279 patients, 66.5% patients became asymptomatic after surgery, symptom improvement was registered in 27.5%, while in 9.1% of patients, no clinical improvement occurred. In 12 studies published after 2010, the percentage of asymptomatic patients reached 73.3%. In addition, it was demonstrated that surgery improved a quality of life and exercise capacity [39]. Residual bronchiectasis and *Pseudomonas aeruginosa* infection were reported as unfavorable prognostic factors [5].

In the same meta-analysis, the pooled mortality from 34 studies with 4788 patients was 1.5%, while the morbidity from 33 studies with 4583 patients was 16.7% [40]. Morbidity was not influenced by year of publication, economic situation, and geographic location. The reported treatment outcome in different surgical series is presented in Table 20.3. Based on the aforementioned evidence, surgery is an effective treatment for localized type of bronchiectasis in highly symptomatic patients.

20.11 Lung Transplantation in Bronchiectasis

Declining pulmonary function with hypercapnia, resting hypoxemia and the need for supplemental oxygen therapy, and recurrent severe bronchial sepsis or significant pulmonary hypertension should lead to referral to the lung transplantation unit [48]. The first successful lung transplantation procedures in bronchiectasis were performed in 1985 in patients with the underlying diagnosis of CF [49, 50]. For CF, lung transplantation has become a well-established therapy in end-stage disease [51].

Little is known about the outcome of lung transplantation (LTx) in non-cystic fibrosis bronchiectasis. In this subgroup, extrapulmonary manifestations as in cystic

Table 20.3 Treatment outcome

	Period	*N*	Excellent	Improved	Not improved	Op mortality	Op morbidity
Sanderson	1952–1967	242	62	24	14	0.4	33
Wilson	1964–1980	84	75	22	4	0	11
Mandaric	1972–1978	145	89	4	7	2	38
Agasthian	1976–1993	134	59	29	12	2.2	25
Ashour	1987–1997	85	74	22	3.5	0	17
Prieto	1988–1999	119	67.6	29	4	0	15
Fujimoto	1990–1997	92	46	38	16	0	20
Balkanli	1992–2001	238	79.4	12	4.6	0	8.8
Kutlay	1990–2000	166	84.7	13.8	1.5	1.7	11
Eren		143	75.9	15.7	8.2	1.4	23
Zhang	2010	790	60.5	14.1	14.8	1.1	16
Hiramatsu	2012	31	100	–	–	0	19
Caylak	2011	339	71	23.3	5.7	0.6	13
Al Rafaelle	2013	138	84.2	15.8	0	0	13
Balci	2014	86	82.5	17.5	0	1.2	14
Valillo	2014	53	98	NR	2	3.8	25

fibrosis are usually not present. Nonetheless, LTx is widely accepted as a treatment option in end-stage bronchiectasis [52]. The preferred procedure is bilateral LTx due to the assumption that infection in the contralateral native bronchiectatic lung would threaten single LTx [53, 54]. Few retrospective studies have examined lung transplantation for bronchiectasis [55–57]. Concerns regarding chronic infection in bronchiectatic airways with multiresistant pathogens exist in the selection of candidates and in post-LTx care. Gram-negative bacteria after lung transplantation were associated with frequent development of bronchiolitis obliterans syndrome (BOS) [58]. *P. aeruginosa* was the most common pathogen after LTx in patients with bronchiectasis [57]. It is suspected that the presence of chronic *Pseudomonas* infection after LTx leads to shorter survival times [57].

In two small studies, the worst survival was observed in patients with the underlying diagnosis of immunodeficiency [57, 59]. Another study found no evidence that transplant recipients with bronchiectasis and antibody deficiency had a poorer prognosis than those with bronchiectasis alone [56]. This question can not still be answered. Chronic lung allograft dysfunction (CLAD)-free survival and BOS development rates in lung transplant recipients with bronchiectasis seem to be comparable with the results for other underlying diseases [57].

The bronchiectasis severity index (BSI) may help in the selection of LTx candidates [60]. So far, there is one single retrospective study testing the BSI to answer this question [57]. All patients had a high BSI score. Further multicenter studies are needed in this field. The outcome of lung transplantation for bronchiectasis is comparable to lung transplantation for other conditions with regard to survival and CLAD-free survival. Lung transplantation is an option for end-stage bronchiectasis.

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An Overview of Bronchiectasis in Children

21

Alexander Moeller and Ahmad Kantar

21.1 Aetiology

Bronchiectasis in children may be the result of chronic or repeated episodes of environmental insults, probably superimposed on a background of genetic vulnerability or increased susceptibility. The majority of children with bronchiectasis suffer from an underlying disorder, see Fig. 21.1.

The term protracted bacterial bronchitis (PBB) has recently been defined for children presenting with chronic wet cough (>4 weeks), positive bronchoalveolar lavage (BAL) fluid cultures for respiratory bacterial pathogens (≥104 CFU/ml) and a cough resolution after a 2-week course of oral amoxicillin-clavulanate [1].

Some children with chronic wet cough present with the clinical picture of bronchiectasis but do not show radiological evidence of bronchiectasis in the chest CT scan. For such children, the term chronic suppurative lung disease (CSLD) has been proposed [2].

The clinical pictures of PBB, CSLD and bronchiectasis are overlapping entities, but from a pathophysiological point of view, it might well be that these conditions are part of a spectrum of symptoms reflecting disease progression [3] (see Fig. 21.2).

Since its earliest recognition by Lannec in 1985, bronchiectasis has been described in early childhood. A distinguishing description of bronchiectasis in children was reported in 1905 by Riviere [4]. The aetiology of these 33 cases was bronchopneumonia, bronchitis with or without whooping cough, measles or diphtheria. The author reported that these changes showed a common origin "from the

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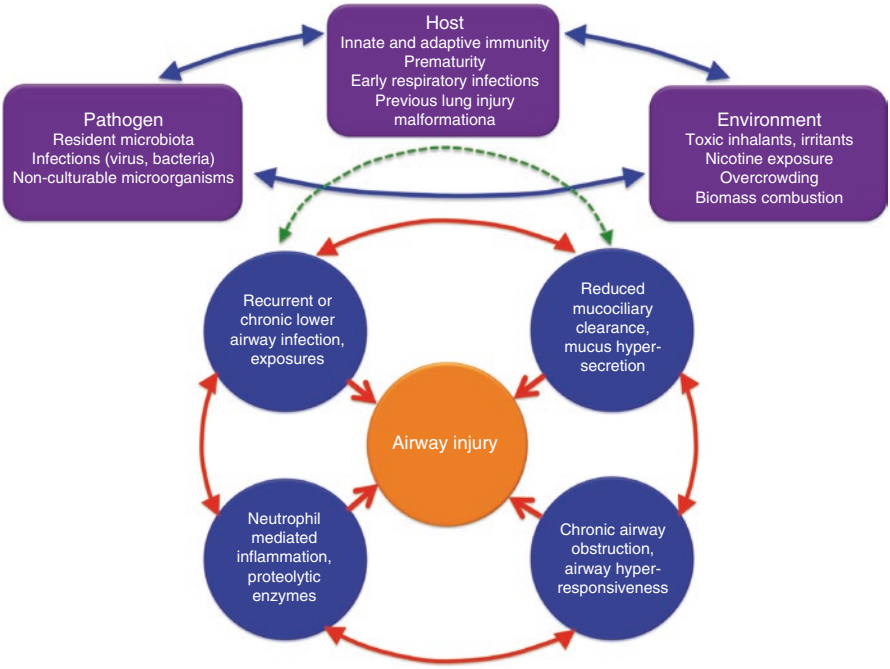

Fig. 21.1 Pathophysiology of bronchiectasis in children

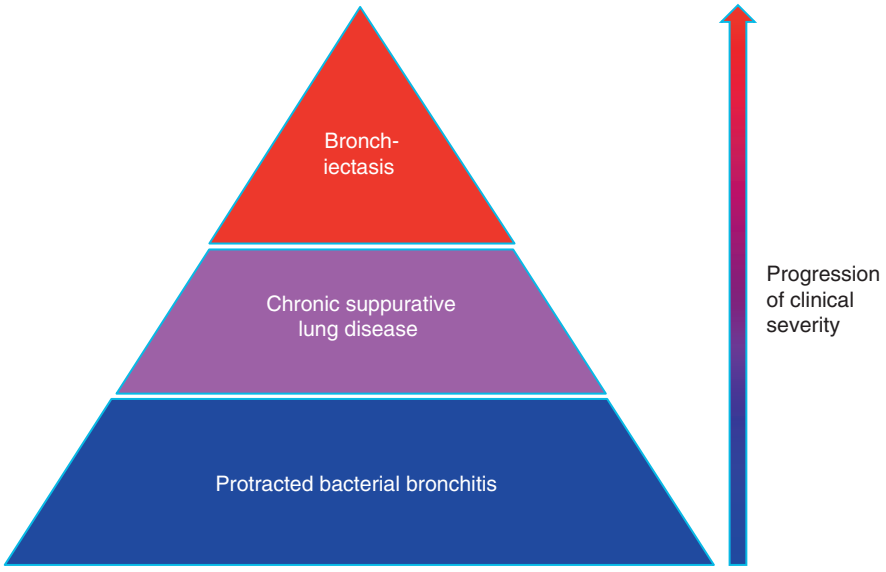

Fig. 21.2 Bronchiectasis in children as part of spectrum of suppurative lung disease

inflammatory lung diseases of childhood, particularly in association with the infective catarrhs of measles and whooping cough". A substantial investigation of the infectious background of bronchiectasis was later provided by Boyd in a report of 56 cases of bronchiectasis observed at the Hospital of Sick Children in Toronto [5]. Among the causative factors, Boyd reported bronchopneumonia, recurrent or chronic bronchitis, pertussis, measles and influenza. Cultures from lung aspiration or suction revealed, in some of the cases, the presence of B-haemolytic *Streptococcus*, *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Spirochetes* and *Fusiform* bacilli. The authors noted that the main factors determining bronchiectasis development were obstruction of the airways and infection. These factors were identified as crucial factors for the development of bronchiectasis. Increased knowledge regarding cystic fibrosis (CF), generalized vaccination programmes and major control of tuberculosis infections in developed countries have decreased the level of attention on bronchiectasis in paediatric ages, down-rating it as an orphan disease in non-CF patients.

The high prevalence of non-CF bronchiectasis (hereafter referred to as bronchiectasis) in indigenous communities from developed countries and the recent surge of awareness of protracted bacterial bronchitis over the last 10 years have revitalized the interest in this field. The incidence of childhood bronchiectasis decreased significantly in most developed countries due to better immunization status and nutrition, higher hygiene standards, reduced crowding and easier access to health care. However, bronchiectasis in children remains common in developing countries and among disadvantaged indigenous populations [6, 7].

The underlying causes of bronchiectasis in childhood vary. However, what should be emphasized is the peculiarity of the response to the different types of insults in paediatric age. The structural changes in the growing lung include alveolar growth and multiplication, vascular development, growth of the airways and maturation of the airway wall structures, all of which are influenced by the simultaneous growth of the thoracic cage [8]. In addition, the immunological response undergoes developmental and memorial processes that make infection the overwhelming cause of diseases in childhood. Moreover, children are more vulnerable to various environmental factors [9].

Effective airway clearance depends from various factors including effective ciliary function, optimal mucus rheology, normal airway size and function and an adequate cough function. Absent or dyskinetic ciliary function as a result of a primary defect (primary ciliary dyskinesia; PCD) or as secondary consequence of chronic inflammation or exposures lead to mucostasis within the airway system. Diseases affecting mucus rheology such as CF and asthma but also chronic bacterial infection lead to ineffective mucociliary transport. Airway malformation and obstruction hinder effective mucus transport but interferes also with cough clearance. The latter, in addition to respiratory muscle weakness and rib cage deformities, is the main problem in children with neuromuscular diseases and cerebral palsy. Each of these basic issues leads to ineffective airway clearance resulting in mucus accumulation within the airways.

Subjects with bronchiectasis seem to fail to restore efficacious mucociliary clearance. By employing radioaerosol inhalation lung cine-scintigraphy studies, Isawa et al. have observed that the transport of inhaled radioactivity from the bronchiectatic regions is greatly deranged [10]. They described regional stasis, regurgitation, reversed transport, straying and spiral or zigzag motion in these areas that may contribute to future worsening.

Respiratory bacterial pathogens within the lower airways may create protective biofilms to overcome host clearance mechanisms and reduce its in vivo susceptibility to antibiotics [11]. Moreover, they secrete toxins that damage ciliary structure and functions and may modulate mucin production [12]. Proteolytic enzymes and oxygen radicals released from activated neutrophils eventually overwhelm lung anti-protease and anti-oxidative defences and begin to digest bronchial wall matrix proteins. In this process of tissue damage, defective regulation of inflammation resolution and injured tissue repair induce irreversibility of the damage itself [13, 14]. This reiteration would result in bronchial dilatation, increased mucus retention, airflow obstruction and the establishment of bronchiectasis.

The onset of structural lung disease in children with CF, diagnosed by neonatal screening, has been intensively investigated in the recent years, resulting in a growing body of evidence on structural lung damage as early as 10 weeks of age [15–19]. Two large Australian cohort studies have shown evidence of bronchiectasis in CT scans of 50–70% of children with CF at the age between 3 and 5 years [15, 17, 20]. Neutrophilic inflammation and pulmonary infection are risk factors for early structural airway damage and lung disease [15–17]. In a recent study, Sly et al. [21] analysed data from 127 infants with a neonatal diagnosis of CF within the Australian Respiratory Early Surveillance team for CF (AREST-CF) study. They found evidence of bronchiectasis in nearly 30% of infants at the age of 3 months increasing to 61.5% at the age of 3 years. Risk factors for the early development of bronchiectasis were analysed from the available clinical and laboratory data by multivariate analyses. Significant risk factors for the detection of bronchiectasis between 3 months and 3 years of age were meconium ileus at presentation, respiratory symptoms at the time of CT scan and invasive assessment (BAL), evidence of air trapping in the expiratory chest CT scan and detection of neutrophil elastase activity in the BAL fluid, with odds ratios ranging between 2.05 and 3.17. A risk factor for persistent bronchiectasis (present on two or more sequential scans) was the detection of free neutrophil elastase activity with odds ratio of 7.2 at 12 months and 4.21 at 3 years of age [21]. In a further study within the AREST-CF population, Garatt et al. showed that a higher ratio for matrix metalloproteinase 9 to tissue inhibitor of metalloproteinase (MMP-9/TIMP-1) was associated with increased levels of free neutrophil elastase in the BAL fluid and bronchiectasis [22]. Neutrophil elastase in expectorated sputum samples from a large cohort of CF patients aged 6 years and older was negatively correlated to lung function (i.e. FEV1), confirming the clinical relevance for CF-associated lung disease [23]. In a small group of children with non-CF bronchiectasis, the severity of bronchiectasis (HRCT severity score) was associated with sputum IL-8 and TNF-αn a small [24].

A recent systematic review determined the specific aetiologies and their relative prevalence among children with non-CF bronchiectasis. The authors selected 12

Table 21.1 Associations of bronchiectasis in children (from [25])

Association	Total number	% of total
No association	308	34
Infectious	174	19
Primary immunodeficiency	158	17
Aspiration/foreign body	91	10
Primary ciliary dyskinesia	66	7
Congenital malformation	34	4
Secondary immunodeficiency	29	3
Asthma	16	2
Bronchiolitis obliterans	12	1
Skeletal diseases others	11	1
Others	7	1

studies comprising 989 children [25]. The size of these studies ranged from a population of 22 to 151 children and encompassed 9 different countries in different continents. Whereas the great part of the studies included children from one to two clinical sites, only one study assessed data from a large regional database.

Among 308 children (34% of total), no association with an underlying condition was reported; hence, the bronchiectasis was of unknown or non-specific origin. The most common associations were infection (n = 174; 19%), primary immunodeficiency (n = 160;18%), recurrent aspiration in neurodevelopmentally impaired children and aspiration of foreign bodies (n = 95; 10%) and primary ciliary dyskinesia (n = 91; 10%) (see Table 21.1).

Severe viral or bacterial pneumonia accounted for 61% of the associations with infection. Besides tuberculosis (11%), measles (14%) was a quite common underlying condition in children with non-CF bronchiectasis. Other infections, including pertussis (5%), interstitial pneumonia (3%), varicella zoster (3%), allergic bronchopulmonary aspergillosis (ABPA) (2%), adenovirus (1%) and neonatal pneumonia (pneumonia at age <6 months) (1%), were much less frequent. In children with primary immunodeficiency, the most common aetiology was a B-cell disorder, accounting for 74% of cases, whereas 10% suffered from a combined immunodeficiency. Among children with CPAM, tracheoesophageal fistula was the most frequent underlying disease accounting for 52% of cases. Cystic lung disease (19%) and bronchogenic cyst (7%) were other relevant aetiologies. The high number of "idiopathic" non-CF bronchiectasis, highlighted in this review, may be due to insufficiently defined diagnostic approaches [25].

As this review reported only retrospective data, misidentification in some cases cannot be excluded, due to variable definitions in the broad range of countries and centres where the studies have been performed, so there is the need for prospectively collected data within a well-structured registry.

A more recent retrospective analysis in a single Indian centre revealed very similar numbers. An underlying aetiology was identified in 64% of 80 children with non-CF bronchiectasis. Postinfectious cause was found in 24% (post TB in 10%), PCD in 15%, ABPA in 7.5%, primary immunodeficiency in 6.2%, malformations in 4%, aspiration in 2.5% and foreign body retention in 1.2% of the cases, respectively [26].

21.2 Microbiology in Children with Bronchiectasis

Non-typeable *Haemophilus influenzae* (NTHi) is the main bacterial pathogen in respiratory samples (upper airway, sputum or BAL) collected from children with non-CF bronchiectasis, followed by *Streptococcus pneumoniae* and *Moraxella catarrhalis* [27, 28]. *Pseudomonas aeruginosa* is uncommon in young children, and, as well as to *Staphylococcus aureus*, the possibility of CF should be considered when these bacteria are detected. Nontuberculous mycobacteria and *Aspergillus* species are rarely reported in children [29].

Recently, Wurzel et al. have prospectively followed for 2 years 106 children with PBB identifying *H. influenzae* infection as a major risk factor with more than seven times higher risk of bronchiectasis development (hazard ratio, 7.55; 95% CI, 1.66–34.28; $P = 0.009$) compared to those without *H. influenzae* infection [30]. It is not clearly understood why NTHi appears to be commensal in the pharynx, and, at the same time, it could be an important respiratory mucosal pathogen in the lower respiratory tract. The host immune response is likely to be a critical factor in preventing NTHi from causing and/or contributing to bronchiectasis development. *H. influenzae* colonizes the nasopharynx early in life, and there is significant turnover of different strains, particularly in young children. Children may be colonized with multiple different strains simultaneously. The role of this colonization in the upper airway microbiome is not well understood (Table 21.2).

Viruses have been historically implicated in the pathogenesis of bronchiectasis. A retrospective study of 193 Canadian children with human adenovirus (HAdV) infection showed the presence of bronchiectasis in 8 of the 10 children who subsequently underwent a chest computed tomography (CT) scan for clinical reasons [31]. In addition, HAdV-C species have been recently detected in the lower airways of children with PBB and bronchiectasis [32]. Moreover, HAdV-positive BAL was significantly associated with bacterial coinfection with *H. influenzae, M. catarrhalis or S. pneumoniae* (odds ratio [OR], 3.27; 95% confidence interval, 1.38–7.75; $P = 0.007$). Viral infection can impair immune responses, enhance bacterial coinfection and induce inflammatory reaction [33].

Table 21.2 Mechanisms employed for *Haemophilus influenzae* infection of the respiratory tract (from [12, 29])

Main mechanism of *Haemophilus influenzae* invasion and persistence in the human respiratory tract
Expressing multiple adhesins with individual specificities for various cell types within the respiratory tract
Intracellular survival within macrophages or epithelial cells
Undergoing antigenic drift
Forming biofilms
Secreting proteases (such as IgA protease)
Reducing ciliary beat
Producing substances that can damage cilia
Modulating mucin production
Inducing host airway inflammatory responses
Producing B-lactamase

21.3 Diagnosis

The definition for bronchiectasis as "irreversibly dilated peripheral airways" was originally based on pathology, but nowadays the same criteria are used for high-resolution chest CT scans [34]. The radiologic diagnostic criteria are described elsewhere. Bronchiectasis should be suspected in any child with prolonged wet cough and no resolution after a prolonged antibiotic therapy [35], but also in children with recurrent lower respiratory tract infections.

Clinically, children with bronchiectasis present continuous wet cough or recurrent episodes of wet cough responsive to antibiotic treatment and/or recurrent chest infections leading to disease exacerbation. Older children may show productive cough with expectorations of intermittently purulent sputum. Symptoms may be aggravated with physical activity, leading to limited exercise tolerance. Crackles may be found on auscultation, but their absence does not exclude bronchiectasis. Clubbing and haemoptysis are rare findings [36].

Chronic wet cough is a major symptom of endobronchial infection, and it is associated with a high burden of illness. There is evidence from BAL studies for lower airway neutrophilic inflammation and bacterial infection and a significant portion of the children with chronic wet cough will respond to a sufficiently long course of systemic antibiotics [37–40].

Recently, a multicentre study involving 326 children newly referred for chronic cough assessed specific cough pointers according to an established clinical algorithm [41]. Out of those 286 children who received treatment specific for their cough and fulfilled the a priori-defined criteria for specified aetiologies, 10% showed bronchiectasis in the chest HRCT scan. The odds ratio for wet cough as a predictor for bronchiectasis was 527 (95% CI 45.4–6102). Reported median (IQR) duration of cough was 27 (7.3, 52.0) weeks.

A recent study by Goyal et al. retrospectively analysed multi-detector chest CT scans of 144 children with chronic wet cough and a prolonged (≥4 weeks) course of oral antibiotics according to a centre-specific clinical management algorithm [35]. CT scans showed evidence of bronchiectasis in 106 subjects. A poor response to the antibiotic therapy was significantly associated with the detection of bronchiectasis, with positive and negative predictive values of 83.8 (95% CI 74.3–90.3) and 75% (95% CI 53.2–90.2), respectively. In addition, duration of wet cough for more than 12 months and indigenous ethnicity were both independent risk factors for underlying bronchiectasis [35]. Interestingly, in this study, co-morbidities such as previous pneumonia, immunodeficiency or congenital pulmonary airway malformation (CPAM) were not significant predictors for the presence of bronchiectasis in the multivariate analysis, probably due to the relatively small proportion of such children [35].

Table 21.3 describes symptoms and signs that should lead to a suspicion of bronchiectasis in children.

It is important to note that there is a continuum between CSLD and potentially reversible airway injury leading to the development of bronchiectasis. Therefore, children with symptoms of CSLD should be assessed and managed as those with

Table 21.3 Symptoms of suspected bronchiectasis [42]

Chronic wet/productive cough especially between viral colds and lasting ≥ 8 weeks
Asthma that does not respond to treatment
Incomplete resolution of a severe pneumonia
Recurrent pneumonia or lower airway tract infection
Pertussis-like illness failing to resolve after 6 months
Persistent and unexplained physical signs (i.e. persistent lung crackles) or chest radiographic abnormalities
Respiratory symptoms in children with structural or functional disorders of the oesophagus and upper respiratory tract
Unexplained haemoptysis
Exertional dyspnoea in non-asthmatic children

Table 21.4 Assessments in children with a new diagnosis of bronchiectasis [42, 43]

Culture of airway secretions (BAL or sputum)
Lung function measurements (spirometry) (≥5 years)
Sweat test and/or genetic analysis
Test of immune and autoimmune function
Allergy test
Test for primary ciliary dysfunction
Nasal endoscopy
Bronchoscopy (airway abnormality, foreign body)
Test for pulmonary aspiration
Test for tuberculosis

radiologically confirmed bronchiectasis, in order to prevent the further development of irreversible airway damage [3].

Children with a clinical suspicion of bronchiectasis should receive a chest HRCT scan to confirm the diagnosis and to assess the severity and extent of disease [43] and should undergo further baseline investigations (Table 21.4).

21.4 Management of Bronchiectasis in Children

Besides the control of symptoms and reduction of exacerbations, the prevention of progressive lung damage and the facilitation of normal growth and lung development are the mainstays of management of bronchiectasis in children. The identification of the underlying aetiology of bronchiectasis is essential and should therefore be stressed. In a study by Li et al., 136 children aged between 3 and 18 years with non-CF bronchiectasis underwent extensive investigations. In 91 children with PCD, recurrent aspiration and immunodeficiency were diagnosed as underlying aetiologies, and in 77 children (56%), management was changed according to the identification of the cause [44].

As there are only a few studies available, the management of non-CF bronchiectasis in children is usually based on the knowledge from CF care. Regular follow-up visits in secondary care should include assessment of growth, optimization of nutrition, maintenance of immunizations and education of patients and parents to

Table 21.5 Cornerstones of therapy

1. Airway clearance techniques, chest physiotherapy and exercise
2. Inhaled therapy and mucoactive drugs
3. Antibiotic therapy
4. Surgery

understand the principles of disease management, recognition of an exacerbation and avoidance of environmental toxic exposures such as nicotine exposure [42, 43].

The therapeutic management is based on the improvement of mucociliary clearance by chest physiotherapy and the promotion of exercise, aerosol therapy, prompt treatment of recurrent exacerbations and correct management of complications (Table 21.5).

21.5 Airway Clearance Techniques, Chest Physiotherapy and Exercise

There is a broad agreement that the regular application of airway clearance techniques and chest physiotherapy may improve airway clearance. However, there is no data to support one method over the other. In infants and preschool children, more passive procedures such as postural drainage are used, whereas in young school children, chest physiotherapy and oscillatory positive expiratory pressure devices (such as Flutter®, Cornett®, Acapella®) are introduced. In older school children, specific breathing manoeuvres are applied including huffing, active cycle of breathing or autogenic drainage, often in combination with postural drainage and aerosol therapy. Regular physical activity and exercise are actively promoted [42, 45].

21.5.1 Inhaled Therapy and Mucoactive Drugs

Despite being regularly used, there is no clear evidence from controlled studies of aerosol therapy efficacy in children with non-CF bronchiectasis. Bronchodilators such as salbutamol may be useful in children with reversible airway obstruction or bronchial hyperreactivity, based on improvement in lung function and/or symptoms [42]. There is no evidence that long-acting bronchodilators or anticholinergic drugs, such as ipratropium bromide, are useful on a regular base, but these drugs can be indicated on an individual level [46–48].

Hyperosmolar agents such as hypertonic saline solution in concentrations between 3% and 7% are effective in this patient population, acting in a multimodal way: (1) to break ion bindings and reduce cross-links of mucin polymers [49]; (2) thanks to the salt, reduce entanglements between mucin and other molecules within the mucus by shielding charges in the mucin polymers [50]; (3) due to his osmotic effect, lead to increased gel-depth aiding cough clearance [50]; and (4) release mediators for ciliary motility by the hyperosmolarity of the airway surface liquid

[51]. The use of inhaled hypertonic saline solution in children is safe, and efficacy has been proven in children and adults with CF [52–54]. In adults with non-CF bronchiectasis, the addition of hypertonic (7%) saline solution to physiotherapy resulted in a significant increase in sputum weight and reduction in sputum viscosity. Although there are no controlled studies in children, this therapeutic option may be considered in children with non-CF bronchiectasis. In children with known bronchial hyperreactivity pretreatment with fast (short?)-acting beta-agonists should be suggested [42, 55].

The use of recombinant deoxyribonuclease (rDNAse) in adult patients with non-CF bronchiectasis was associated with higher exacerbation and hospitalization rates and deterioration in lung function, but no data are published in paediatric population. Therefore, this therapy should not be considered [42, 43]. Asthma medication such as inhaled corticosteroids should not be routinely used but may be indicated in individual patients with bronchial hyperreactivity and or concomitant asthma [42, 43].

21.6 Antibiotics

As bacterial colonization and infection play a central role in the pathophysiology of bronchiectasis, antibiotic therapy is recommended in the management of this condition. Mild exacerbations may be treated with oral antibiotics, whereas intravenous administration, combined with intensive chest physiotherapy, is recommended in severe exacerbations. Duration depends on the severity and response to treatment and is usually between 2 and 4 weeks. Ideally, antibiotics are prescribed according to airway cultures and susceptibility results from sputum, throat swabs or BAL. Empirical therapy is started in severe acute deteriorations and if no recent microbiology cultures are available. However, if possible, airway specimens should be collected prior to commencing antibiotic therapy. Short antibiotic courses have been shown to improve quality of life and reduce symptoms and inflammation [56]. In most children, first-line empirical therapy is amoxicillin or amoxicillin-clavulanic acid in those children with a history of β-lactamase. Common pathogens in bronchiectasis, such as *Haemophilus influenzae* and *Streptococcus pneumoniae*, show high level of resistance to macrolides; however, macrolides have anti-inflammatory properties and are therefore often used. Oral ciprofloxacin should be used in patients with known airway colonization with *Pseudomonas aeruginosa*. Intravenous antibiotics are considered in children if oral therapy has failed, especially when resistant organisms or microorganisms are not responsive to oral treatment, such as *P. aeruginosa* [42, 43]. Intermittent oral antibiotic therapy to reduce the bacterial burden has not been evaluated so far.

Long-term antibiotics may be preventive for further airway damage in children with CSLD and early bronchiectasis to limit the progression of the disease. Azithromycin, clarithromycin, amoxicillin-clavulanic acid and co-trimoxazole are used for long-term therapy, but there are no longer-termed studies to suggest preference of one of the regimes [42].

A multicentre, double-blind, randomized, parallel-group, placebo-controlled trial by Valery et al. [57] assessed the efficacy and safety of azithromycin (30 mg/kg) or placebo once a week for up to 24 months in 89 Indigenous Australian, Maori and Pacific Island children aged 1–8 years with CSLD or bronchiectasis. Only children with a least one exacerbation in the previous year were included. The primary outcome of this study was the exacerbation rate defined as clinical worsening needing antibiotic therapy. At the beginning and at the end of the study, airway cultures obtained by means of a nasal swab were analysed for antibiotic resistance development. The study was terminated early due to feasibility constraints leading to a mean treatment duration of 20.7 months. Children on azithromycin showed a significantly reduced exacerbation rate as compared to those receiving placebo (incidence rate ratio 0.5; 95% CI 0.35–0.71, $p < 0.0001$). In addition, carriage of both *H. influenzae* (37% and 25% vs. 7% and 38% at study end, respectively) and *M. catarrhalis* (17% and 16% at start vs. 0% and 24% at end, respectively) was significantly lower in the azithromycin group compared with placebo. However, more children of the active group showed carriage of azithromycin-resistant bacteria at the end of the study (46% vs. 11%, respectively, $p = 0.002$) [57].

Long-term use of macrolides results in resistance particularly to *Streptococcus, Haemophilus* and *Staphylococcus*. In children with cystic fibrosis, the development of macrolide resistance is well described. Within a 4-year period, erythromycin resistance in *Staphylococcus aureus* increased from 6.9% to 53.8% and clarithromycin resistance in *Haemophilus* spp. increased from 3.7% to 37.5% in children on long-term azithromycin maintenance therapy in a Dutch CF centre [58]. In another study, macrolide resistance in *Staphylococcus* increased from 10% before initiation of long-term azithromycin therapy to 83% within 1 year and to 100% after the third year [59].

Whilst there is a large body of evidence for the use of inhaled tobramycin in treating chronic infection or for the eradication upon a first appearance with *P. aeruginosa* in CF patients, there is insufficient evidence for the use of inhaled antibiotics in children with non-CF bronchiectasis. Twiss et al. have shown that inhaled gentamycin was well-tolerated and yielded bactericidal concentrations in sputum with negligible systemic absorption in children with non-CF bronchiectasis [60]. Although there is no controlled study for the use of inhaled antibiotic, this option may be considered in children with frequent exacerbations and/or progressive bronchiectasis not sufficiently controlled with other therapeutic regimes such as prolonged oral antibiotic treatment or in children with chronic colonization with *P. aeruginosa* [42].

21.7 Surgery

Surgery is rarely indicated and may be limited to cases of focal disease, symptoms which are unable to be controlled by medical therapy, or for the treatment of complications such as haemoptysis, empyema or lung abscess.

In geographical regions with scarce access to health care and conservative treatment such as chest physiotherapy, the decision to perform surgery may be made to avoid further progression and or dissemination of bronchiectasis [61]. With the improvements in perioperative management and surgical techniques, complications are less frequent and postoperative results have improved [62].

A recent retrospective analysis included 109 consecutive children (1–15.5 years) undergoing a total of 123 surgical procedures (resections) for bronchiectasis in Brazil. As per protocol, the indication for surgery was made when there was an insufficient response to physiotherapy and antibiotics given during exacerbation or over prolonged periods if indicated. Surgery was avoided in children with multifocal bronchiectasis but some selected children underwent resection of the most affected part. Left inferior lobectomy and middle lobectomy were the most frequent interventions (38% and 24%, respectively). During the follow-up 61% of the children showed clear clinical improvement, 14% did not improve whilst 24% were lost for follow-up [62]. Another retrospective study included 35 children aged 1–9 years in Turkey. In these children, lobectomy was performed in 17 patients (48.5%), pneumonectomy in 7 (20%), lobectomy plus segmentectomy in 5 (14.2%), bilobectomy in 2 (5.7%) and segmentectomy in 4 (11.4%). During a mean follow-up time of 5.5 ½ years, two thirds remained asymptomatic, whereas 25% improved clinically and 11% showed no improvement. Complete resection was associated with better clinical outcome [63].

21.8 Prevention

Even in those children predestined to develop bronchiectasis, airway damage can be limited by intense treatment and reduction of detrimental exposures. Therefore, children with a high risk for developing bronchiectasis such as mucociliary disorders, immune dysfunction and rheumatic inflammatory conditions should undergo a careful and regular clinical follow-up. Vaccinations for measles, *Bordetella pertussis*, *S. pneumoniae*, *H. influenzae* and *influenza* play an important role in the primary prevention. The development of irreversible airway damage in children with CSLD and the progression of bronchiectasis can be reduced also by implementing these strategies in addition to early, appropriate treatment of exacerbations and reduction of exposures [64].

Early and intensive treatment improved lung function in 59 children (age 4.8–15.8 years) with reduced FEV1 at diagnosis and prevented deterioration in the following 2–5-year follow-up period [65].

The frequency of exacerbations requiring hospitalization was a significant predictor of FEV1 decline during a 3-year follow-up in 52 children with a decrease of 1.95% in FEV1% predicted with each exacerbation [66].

In a Turkish study of 111 children, “intensive medical treatment” (prompt antibiotic use, physiotherapy, bronchodilators) reduced exacerbation rates from 6.6 ± 4 to 2.9 ± 2.9 per year [6].

21.9 Why Bronchiectasis in Children Is Different than in Adults?

King et al. investigated 182 subjects with bronchiectasis and distinguished two phenotypes of patients with bronchiectasis who had developed a chronic productive cough in childhood (before 16 years of age) compared with those who had developed a productive cough as adults [67]. In the childhood-onset group, 24% of the subjects had a potentially causative factor identified, such as being postinfectious, an IgG subclass deficiency, ABPA, PCD and Young's. The clinical features of the childhood onset and adult onset groups differed in several factors. The median duration of the productive cough was tenfold longer in the childhood-onset group ($p < 0.001$). The volume of the daily sputum production was also higher in the childhood-onset group, but this did not achieve statistical significance. The prevalence of haemoptysis showed a trend to be higher in the childhood-onset group, possibly reflecting increased airway inflammation. The incidence of rhinosinusitis was almost threefold higher in the childhood group. The childhood-onset group had more than three times the prevalence of crepitation, possibly reflecting the increased sputum production. Moreover, the authors observed that there was also a bimodal distribution of age onset with the onset of a productive cough most common in the first 15 years of life followed by the onset of a productive cough in subjects over the age of 50. There were relatively few subjects who developed the onset of a productive cough between the ages of 16 and 50 years. These findings suggest that immune function is best during this time lapse and then declines [68].

More interestingly, Field reported that as children became adults, their symptoms improved regardless of the treatment [69].

Mucins are the main macromolecular component of the mucus gel in health. They are glycoproteins responsible for the protective and clearance properties of the mucus. The biophysical and biochemical characteristics of mucus in adults have been commonly investigated, but there is much less knowledge regarding children [70]. Submucosal glands, which are present wherever there is cartilage, are located mainly in the submucosa, between the cartilage and surface epithelium, and are responsible for producing most of the mucus in the large airways. In a normal adult, it is reported that the area occupied by the gland constitutes approximately 12% of the wall; however, in children, that area is approximately 17%. This difference suggests that mucus hypersecretory states might be of greater consequence in children than adults [71, 72].

An integral aspect of human development is the acquisition of our microbiota. The composition of the gut microbiota is unstable in the first 3 years of life. Following initial colonization, the maturation of microbiota involves an increase in diversity and stability; communities undergo several consecutive changes until an "optimal" community is acquired [73, 74]. Modification of this process can have diverse effects on other organs and systems, including the immunological systems [75]. The lung microbiome is subject to continuous invasion by agents from the upper airways by phenomena, such as inhalation or microaspiration. These

Table 21.6 Factors that determine the differences between children and adults and increase the risk for bronchiectasis

Factors	Differences between children and adults
Airways	Anatomy, structure and function
Mucus	Mucus secretion
Immune system	Immune maturity, immune memory
Microbiota	Microbiota composition
Environmental insults	Increase effect of pollution
Infectious diseases	Immunological response and immunization against infection

processes are opposed by the unceasing elimination and neutralization by mucociliary defence, cough and the host immune system (both innate and adaptive). During disease, the regional growth conditions of the lungs change dramatically, creating permissive niches for selective bacterial reproduction [76].

A recent study compared microbiota among three different paediatric cohorts (CF, protracted bacterial bronchitis or bronchiectasis), and the results were compared with those obtained from adults CF and bronchiectasis [77]. All three paediatric disease cohorts shared similar core respiratory microbiota that differed from adult CF and bronchiectasis microbiota. The adult with CF and bronchiectasis microbiota also differed from each other, suggesting that the common early infection airway microbiota diverge within individuals by adulthood. These data suggest that clinically distinct chronic airway infections share common early core microbiota, which are likely shaped by natural aspiration and impaired clearance of the same airway microbes but whose disease-specific characteristics select for divergent microbiota by adulthood (Table 21.6).

Conclusions

Multiple genetic, anatomical and systemic causes of bronchiectasis have been identified [78]. Regardless of the underlying causes of bronchiectasis, they share the common denominator of mucus retention and superimposed bacterial colonization. The mechanism underlying lung damage seems quite similar. Protracted, persistent or recurrent infections and amplified neutrophilic inflammation are the basis of lung injury. These are typically associated with impaired mucociliary clearance and poorly regulated inflammatory responses. Excessive inflammation can persist after the infection is controlled [28, 79].

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