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REVIEW

Management of Bronchiectasis in Adults

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ABSTRACT

Bronchiectasis is a highly heterogeneous disease in its clinical presentation, severity and treatment response, making the therapeutic approach challenging. The field has benefited greatly from the introduction of evidence-based guidelines, but most recommendations are based on low-quality evidence.

The treatment goals in bronchiectasis are to improve airway clearance, prevent or suppress chronic airway infection and reduce airway inflammation. Reducing the airway inflammation might be the ultimate goal of bronchiectasis treatment, avoiding exacerbations and minimizing antibiotic exposure.

A deeper understanding of the pathophysiology of bronchiectasis is an unmet need, focusing on the inflammatory pathways, the role of the microbiome and dysfunctional mucociliary clearance. This will allow the identification of disease endo-phenotypes and the development of personalised therapeutic approaches.

This review provides an update on the management of bronchiectasis highlighting emerging evidence from recent randomised trials and future perspectives.

Keywords: Antibiotics. Bronchiectasis. Endotype. Infection. Inflammation.

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INTRODUCTION

Bronchiectasis is a common chronic respiratory disease characterised by a clinical syndrome of cough, sputum production and respiratory infections, and radiologically by abnormal and permanent dilatation of the bronchi[1]. Once considered as a neglected "orphan" disease, recent years have seen renewed interest, resulting in more clinical research and the development of new treatments[2]. Bronchiectasis incidence and prevalence are increasing worldwide, particularly in older age groups, with data from the United Kingdom revealing rates of 485 per 100,000 in men, and 566 per 100,000 in women[3]. Quint et al.[3] also described that mortality, independent of age, is more than twice the mortality in the general population. Some longitudinal studies have described a one-year mortality of around 30% after suffering a severe exacerbation requiring hospitalisation[4,5]. The impact on healthcare systems is substantial, and increases with disease severity, hospitalisations, need for intensive care, and use of inhaled antibiotics[1].

The pathophysiology of bronchiectasis is not yet fully understood, but the vicious cycle hypothesis was first proposed by Cole[6]. Since disease progression is linked to impaired mucociliary clearance, airway bacterial colonisation, airway inflammation and airway structural damage, therapies in bronchiectasis have traditionally targeted a point to "break the cycle"[7]. However, given the lack of cure in transiently breaking this cycle associated to high degree of clinical heterogeneity, a multimodal therapy approach aiming to address all aspects of the disease might be more fitting[8].

No pharmacological treatments have been licensed by regulatory agencies worldwide, and most therapies used in clinical practice are based on limited evidence due to a lack of randomised trials[9]. Emerging evidence shows that bronchiectasis is a heterogeneous disease with many different biological mechanisms driving progression, and therefore the so-called treatable traits approach, used in other chronic lung diseases, could be also applied to bronchiectasis[9,10]. This review provides an update on the management of bronchiectasis, focusing on existing and developing therapies.

DIAGNOSIS AND ASSESSMENT

The treatment of bronchiectasis begins with accurate diagnosis and appropriate assessment of patients. Bronchiectasis should be suspected in patients with chronic cough particularly when accompanied by mucopurulent or purulent sputum production. Fatigue, breathlessness, haemoptysis and chest discomfort are also relatively common symptoms. The diagnosis should also be considered in patients with recurrent respiratory tract infections. It may present at any age from early childhood but is more common with increasing age and in females[11].

High resolution computed tomography (HRCT) scanning is the diagnostic test of choice for bronchiectasis. Chest radiography is insufficiently sensitive to exclude the diagnosis. The diagnostic feature is an increase in the ratio between the bronchial diameter and the adjacent vascular diameter (bronchoarterial ratio > 1). Additional criteria are a lack of normal tapering and visualisation of the bronchi within one cm of the pleural surface[11,12]. HRCT

scanning can also aid in identifying an underlying aetiology of bronchiectasis, e.g. allergic bronchopulmonary aspergillosis (ABPA) which may demonstrate central bronchiectasis, non-tuberculous mycobacteria (NTM) which may cause nodular bronchiectatic changes most frequently in the middle lobe and lingula, primary ciliary dyskinesia (PCD) typically affecting the middle and lower lobes and may be associated with dextrocardia in around 50% of cases, alpha1-antitrypsin deficiency which may be associated with characteristic emphysema and the presence of a foreign body. HRCT features can also give an indication of the degree of disease activity, evident through the extent of bronchial wall thickening, mucus plugging and additional features such as air trapping or consolidation. It can be useful to repeat the HRCT in a deteriorating patient[12].

Lung function in bronchiectasis can vary widely. Although most patients are believed to have an obstructive lung function abnormality, restrictive or normal patterns can also be seen[13].

Microbiology

Infection is the dominant stimulus for airway neutrophil recruitment and is considered to be a disease progression driver in bronchiectasis[14].

Chronic airway infection occurs predominantly with Gram-negative organisms such as *Haemophilus influenzae*, *Pseudomonas aeruginosa*, *Moraxella catarrhalis* and Enterobacterales, but Gram-positive organisms, such as *Staphylococcus aureus* and *Streptococcus pneumoniae* are also identified in sputum[1,11,15]. Gram-negative infection becomes more frequent as the disease becomes severe, suggesting a progressive impairment in antimicrobial defences. *P. aeruginosa* is the most frequent organism in severe bronchiectasis. Its intrinsic resistance to many antibiotics as well as its ability to form biofilms contribute to its persistence[16]. It is associated with a three-fold increase in mortality risk, an almost seven-fold increase in the risk of hospital admission and an average of one additional exacerbation per patient per year[17]. The prevalence of NTM in bronchiectasis patients is estimated to be around 10% (most frequently *Mycobacterium avium* complex) and should be actively sought by staining for acid-fast bacillus and mycobacterial culture[18,19]. International guidelines suggest that a sputum culture should be sent at least once per year, in order to guide antibiotics both for treatment of acute exacerbations and for chronic suppressive therapy[12].

Bacterial infection is a consistent risk factor for future exacerbations. Not only the presence of bacteria, but also the bacterial load appears to be relevant. In patients with clinically stable bronchiectasis, a higher bacterial load has been identified as a significant predictor of exacerbations (≥ 3) and hospitalisation[14].

The microbiology of bronchiectasis is evolving with sequencing-based technologies allowing the profiling of lung bacterial communities. Recent data showed a progressive reduction in microbiome diversity as the disease becomes more severe. Poorly diverse microbiome profiles and those dominated by *P. aeruginosa* were associated with greater disease severity, higher frequency and severity of exacerbations, and higher risk of mortality. Further research is required to understand the role of the microbiome in bronchiectasis disease progression[20,21].

Underlying cause

The first step following bronchiectasis diagnosis is to identify an underlying cause, however, up to 80% of the patients with bronchiectasis are classified as idiopathic and post-infective[22]. Many of the potentially treatable causes require specific therapeutic interventions and thus a systematic aetiologic evaluation is recommended, for instance, through a standardised aetiological algorithm[23].

The European Respiratory Society (ERS) guidelines recommend an initial screening with differential blood count, serum immunoglobulins (IgG, IgA and IgM) and tests for ABPA (total IgE and specific IgE to *Aspergillus* along with IgG to *Aspergillus* or *Aspergillus* precipitins). Routine sputum cultures should be performed to identify bacterial infection and specific cultures at diagnosis to exclude NTM[1]. A range of other tests may be appropriate in specific circumstances. Antibody responses to the pneumococcal polysaccharide vaccine can help to identify immunodeficiency. Some causes of bronchiectasis such as severe infections, tuberculosis (TB), gastro-oesophageal reflux disease (GORD), inflammatory bowel disease and connective tissue diseases (e.g. rheumatoid arthritis) may be evident from history and physical examination[12]. Testing for cystic fibrosis (CF) should be considered in young adults or those with specific clinic features of the disease such as the presence of upper lobe disease, isolation of *S. aureus* or *P. aeruginosa* and non-pulmonary manifestations suggestive of CF (pancreatitis, infertility and malabsorption). PCD can be suspected if there is a history of neonatal distress, symptoms from childhood, nasal polyposis and/or chronic rhinosinusitis, history of middle ear infections, situs abnormalities and congenital cardiac defects[12].

Immunoglobulin replacement, corticosteroids and antifungals for ABPA, treatment for NTM and of CF represent specific treatment for an underlying cause, reinforcing the importance of systematic testing that is recommended in consensus guidelines[1,12,24].

Besides these underlying treatable causes, there are other comorbidities, environmental and psychological factors, which can also impact patients outcomes being potentially treatable traits[10]. Asthma and chronic obstructive pulmonary disease (COPD) can overlap with bronchiectasis. In clinical practice, it is common to identify patients with both COPD and bronchiectasis, being unclear whether recurrent bronchiectasis exacerbations have led to an obstructive pattern, or whether COPD with frequent exacerbations has led to the development of bronchiectasis[25]. Investigation for bronchiectasis should be considered in patients with COPD with frequent exacerbations and the authors' opinion is that a positive sputum culture for *P. aeruginosa* in a COPD patient, whilst stable, should lead to an HRCT to investigate likely bronchiectasis[12]. Bronchiectasis has been detected in severe asthma in less than 40% of patients who experience frequent exacerbations; it usually has a non-eosinophilic inflammatory pattern that is poorly responsive to standard asthma treatment. In patients with bronchiectasis without asthma history, some "asthma-like features" may be observed[25]. Identification of these phenotypes is of utmost importance, as they require different therapeutic approaches.

Other comorbidities such as chronic rhinosinusitis, depression, underweight and cardiovascular diseases should be recognised as treatable traits in order to address specific treatment[10].

Severity

Bronchiectasis has a broad spectrum of presentation, ranging from mildest disease with almost no sputum symptoms ("dry bronchiectasis") and infrequent exacerbations, to patients with severe symptoms, frequent exacerbations and important lung structural damage. Due to its heterogeneity, disease management can be a challenging task, thus severity assessment and specific scores provide a useful tool for clinical decision making around treatment regimens, morbidity and prognosis[7,13].

In the last 10 years, two multidimensional scoring systems have been developed to predict future mortality: the BSI (Bronchiectasis Severity Index)[26] and the FACED (F – Forced expiratory volume in the first second (FEV_1), A – age, C – chronic infection with *P.aeruginosa*, E – radiological extension, D – dyspnoea)[27].

BSI is a well-validated predictive tool combining age, body mass index (BMI), FEV_1, previous hospitalisation, exacerbation frequency, colonisation status, Medical Research Council (MRC) dyspnoea score and radiological appearance. The score was designed to predict future exacerbations and hospitalisations, health status, and mortality over four years. The predicted risk of hospitalisation at four years varies between 0-9.2% to 41.2-80.4% for mild and severe patients, respectively[26]. This calculation tool is accessible at www.bronchiectasisseverity.com.

The FACED score was originally developed to predict mortality[27]. As exacerbations are an important marker of severity and a stronger predictor of future exacerbations[12], E-FACED score (including the variable "at least one severe exacerbation in the previous year") was created to improve the predictive capacity of yearly exacerbations and hospitalisation[28].

There might be some relevant omissions from both scores, for instance, the Health-Related Quality of Life (HRQoL) and the presence of comorbidities, which are relevant in the prognosis of other chronic respiratory diseases[12,13]. In addition, disease severity is linked with neutrophilic inflammation that has been studied most extensively for neutrophil elastase, a pro-inflammatory compound secreted by airway neutrophils. Elevated sputum neutrophil elastase activity has been associated with a higher BSI score, exacerbation frequency, higher bacterial load and FEV_1 decline[29].

MANAGEMENT OF STABLE PATIENTS

General management

The main treatment goals are to reduce symptoms, improve quality of life, prevent exacerbations and lung function decline and, ultimately, improve survival[1]. The evidence base for most bronchiectasis therapies is weak[1]. As noted above, the identification and treatment of underlying causes is the critical first step in management. Bronchiectasis patients must be encouraged to stop smoking. Annual influenza

and polysaccharide pneumococcal vaccination is recommended according to guidelines[1,12,24]. Coronavirus disease (COVID-19) vaccination is also required for patients with bronchiectasis according to national vaccination schedules (Fig. 1).

Nutritional aspects

Low BMI is common because patients have greater energy requirements due to chronic inflammation and increased work of breathing. A low BMI is an independent predictor of mortality, as noted in the BSI severity tool. Thus, nutritional assessment and intervention should be part of the multidisciplinary management of these patients[24,26].

Airway clearance and rehabilitation

Non-pharmacological interventions are among the most effective means of management of bronchiectasis and include airway clearance techniques (ACT) and pulmonary rehabilitation (PR). Both ACT and PR are proven to reduce symptoms and exacerbation frequency and improve HRQoL. Improving mucus clearance can be sufficient to control disease in a proportion of patients[11]. Consensus guidelines recommend that all patients with bronchiectasis should be taught an ACT by a trained respiratory physiotherapist to perform it once or twice daily[1,12,24].

There are a wide range of ACT consisting of breathing techniques (e.g. active cycle of breathing) sometimes combined with airway oscillatory devices (e.g. flutter or acapella) that modify expiratory flow and volumes or produce chest wall oscillations to increase mucus clearance[30]. Data suggests that ACT lead to improvement in sputum expectoration, reduced hyperinflation as well as improved HRQoL in stable patients[31]. A recent randomised trial from Spain showed large improvements in QoL and less exacerbations with ACT[32]. Since no single ACT has currently shown superior effect over another[12,30], in the authors' opinion, the chosen technique should be tailored to patients' preference, considering that simple techniques will encourage adherence[7]. In the real world, ACT remain significantly underutilized, with data from the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) reporting that only 45% of data registrants perform ACT regularly[30].

PR is strongly recommended by the 2017 ERS guidelines[1], with benefits at least as great in COPD[33,34]. A systematic review confirmed the short-term benefits of supervised PR, but most of the benefits were not sustained to 6 or 12 months suggesting a need for a continuous intervention to achieve long-term benefits[35] Low levels of physical activity are an important risk factor for severe exacerbtions[36].

In the authors' opinion, one of the most effective forms of chest physiotherapy is physical exercise. Thus, interventions to reduce sedentarism should be incorporated in PR programs, but also encouraging physical exercise as part of lifestyle.

Mucoactive therapy

Patients with persistent difficulty with expectoration, despite airway clearance, may benefit

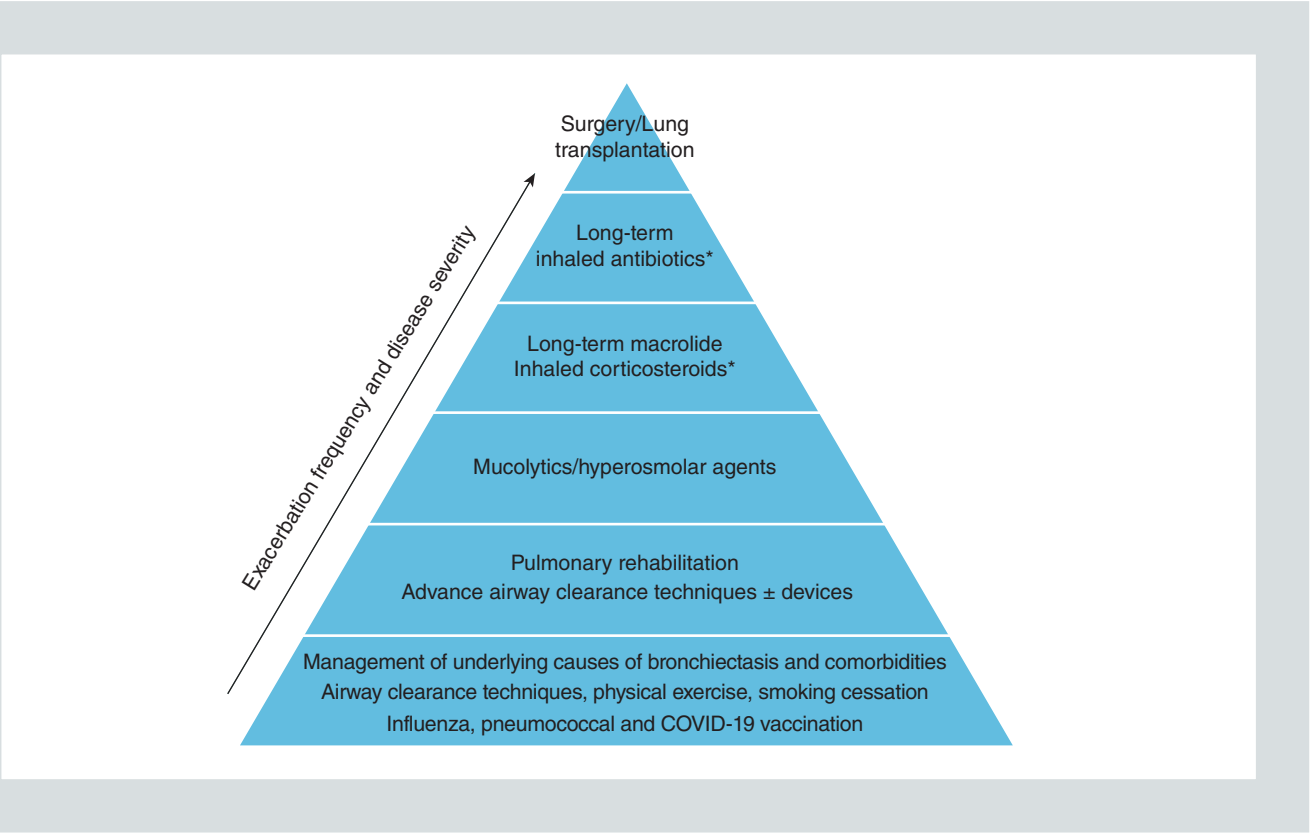

Figure 1. Main components of bronchiectasis management. General interventions are presented on a pyramid base and should be considered for all patients with bronchiectasis, with specific therapeutic interventions for severe disease or frequently exacerbating patients. *Targeted towards specific treatable traits.

from therapies such as nebulised saline solutions, mannitol and mucolytic agents. Isotonic and hypertonic saline can improve cough related quality of life and HRQoL in patients with bronchiectasis in addition to ACT, but it is unclear if hypertonic saline benefits are superior to isotonic[12]. Mannitol did not improve exacerbation frequency; however, it increased the time to first exacerbation, demonstrated a small improvement in QoL and reduced sputum plugging[37,38]. Mucoactive agents, including mannitol but potentially also hypertonic saline, which has a similar mechanism of action, are more effective in patients with more severe symptoms[39]. Recombinant human DNase increased exacerbation frequency and had a small but negative effect on FEV_1; therefore, is contraindicated in bronchiectasis patients[40]. An airway reactivity challenge test should be performed when mucoactive treatment such as hypertonic saline is first administered, and a pre-treatment with a bronchodilator should be considered, especially in patients where bronchospasm is likely (asthma, bronchial hyperreactivity or severe airflow obstruction with FEV_1 < 1L)[12].

Oral mucolytics, such as carbocisteine and N-acetylcysteine, are widely used despite insufficient evidence[1,12,24]. In a small open label randomised trial from China, the long-term use of N-acetylcysteine has been shown to

reduce the risk of exacerbations in bronchiectasis patients, however this study has important limitations[41]. Oral mucoactive drugs may be considered in patients with difficulty expectorating despite practicing adequate ACT. The UK Randomised Open Label Trial of Hypertonic Saline and Carbocisteine in Bronchiectasis (CLEAR) is currently taking place to determine whether hypertonic saline solution and/or carbocisteine can reduce the number of exacerbations over a year compared with standard ACT alone (NCT04140214).

Control infection

Eradication

Eradication treatment refers to antibiotics given to prevent chronic infection with pathogenic microorganisms. This therapy should be considered on the first isolation of *P. aeruginosa*, or exceptionally when a subsequent isolation emerges following a period of negative sputum samples indicating a reinfection[11]. *P. aeruginosa* eradication with oral ciprofloxacin 750 mg *bid* for two weeks, or intravenous antipseudomonal antibiotics plus inhaled antibiotics is the standard of care on the first isolation of *P. aeruginosa*, according to guidelines recommendations[1,12]. Scarce data supports the effectiveness of these different eradication strategies, however, distinct antibiotic regimens resulted in a *P.aeruginosa* 6-month eradication rate of 52%[42] to 73%[43], with a significant reduction in the exacerbation frequency. All of the data in bronchiectasis comes from uncontrolled observational studies and are therefore prone to various biases. The benefit of pathogen eradication beyond *P.aeruginosa* has low evidence[1].

Chronic airway infection

The consensus definition for chronic infection is evidence of positive respiratory tract cultures of the same microorganism, on two or more occasions at least three months apart over one year, while in a stable state[44]. Chronic infection is considered one of the most concerning issues in bronchiectasis management, with evidence that *P. aeruginosa* chronic infection is associated with worst clinical outcomes, such as frequent exacerbations and higher mortality[17,7,28]. For this reason, the management of chronic infections often includes long-term antibiotic therapy.

According to current guidelines, long-term antibiotics should be considered, only, in patients with three or more exacerbations per year, despite optimal therapy. However, this threshold may be reduced in patients with a history of severe exacerbations, with a significant impact on their QoL, in patients with more severe bronchiectasis or relevant comorbidities such as primary/secondary immunodeficiency[1,26]. It is of utmost importance to review adherence to ACT, PR, mucoactive therapy and management of comorbidities before considering to "stepping-up" to long-term antibiotics (Fig. 1). The main therapeutic options for long-term management of chronic infection include inhaled antibiotics and oral antibiotics, such as macrolides.

Inhaled antibiotics have theoretical advantages over oral therapies by delivering higher concentrations of drugs to the airway, reducing systemic absorption and side effects. Inhaled antibiotics reduce airway bacterial load and, consecutively, reduce airway inflammation[45]. In Europe, colistin use has become more widespread due to its broad antibiotic spectrum and

reduced propensity to induce resistance compared to aminoglycosides. A phase 2 clinical trial using nebulised colistin delivered through the "I-neb" device failed to meet its primary endpoint, but showed an improvement in QoL and fewer exacerbations, particularly in cases with good compliance to treatment[46]. Long term efficacy and safety of inhaled colistimethate sodium in bronchiectasis subjects with chronic *Pseudomonas aeruginosa* infection (PROMIS-I), a phase 3 clinical trial of colistin via the I-neb, recently reported a statistically significant reduction of 39% in exacerbations. The full results in the form of a peer-reviewed publication are awaited[47]. Other trials involving dry powder ciprofloxacin (Phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis [RESPIRE])[48,49], and nebulised liposomal ciprofloxacin (Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with Pseudomonas aeruginosa [ORBIT])[50] have not consistently reached primary endpoints. A recent meta-analysis[51] that included these previous trials[46,48-50] revealed that inhaled antibiotics significantly reduced the frequency of all exacerbations (rate ratio = 0.81; 95% confidence interval [CI], 0.67–0.97; p = 0.020). Further, the time to first exacerbation was significantly prolonged (hazard ratio = 0.83; 95% CI, 0.69–0.99; p = 0.028), and the proportion of patients with at least one exacerbation decreased (risk ratio = 0.85; 95% CI, 0.74–0.97; p = 0.015). The use of inhaled antibiotics was well tolerated, with fewer adverse effects such as bronchospasm. The meta-analysis suggests that inhaled antibiotics are effective and safe[51] (Fig. 2) but it is difficult, as shown in the figure, to accurately estimate how effective these drugs are due to inconsistent results. The inconsistent data prompts us to consider reasons for the failure of individual trials, such as patient selection and the use of cyclical regimens with 28-days on/28-days off. This latter point is particularly problematic as airway bacterial load and, therefore, inflammation increases during the off periods resulting in worsening of symptoms[52]. It is the authors' practice to use inhaled antibiotics continuously in all cases to maintain suppression of bacterial load and therefore airway inflammation.

Currently, ERS guidelines suggest first-line long-term treatment with an inhaled antibiotic in patients with bronchiectasis and chronic *P. aeruginosa* infection, who have three or more exacerbations per year, although they can be also used in patients infected with pathogens other than *P. aeruginosa* in whom oral antibiotic prophylaxis is not tolerated, contraindicated or ineffective[1].

A supervised test dose with pre- and post-spirometry is recommended for the first administration of inhaled antibiotics due to the risk of bronchospasm, which occurs in 10-20% of patients treated with aminoglycosides but is much less frequent with colistin. Therefore, prior inhalation of a short-acting bronchodilator is also advisable[1].

Long-term macrolide is the primary oral antibiotic prophylaxis used in bronchiectasis. Macrolides have been studied in randomised clinical trials over the past 10 years. Notwithstanding some differences related to the drugs, doses or treatment duration used in the trials, Effectiveness of Macrolides in patients with Bronchiectasis using Azithromycin to Control Exacerbations (EMBRACE)[53], Bronchiectasis and long-term Azithromycin Treatment (BAT)[54] and Bronchiectasis and Low-dose Erythromycin

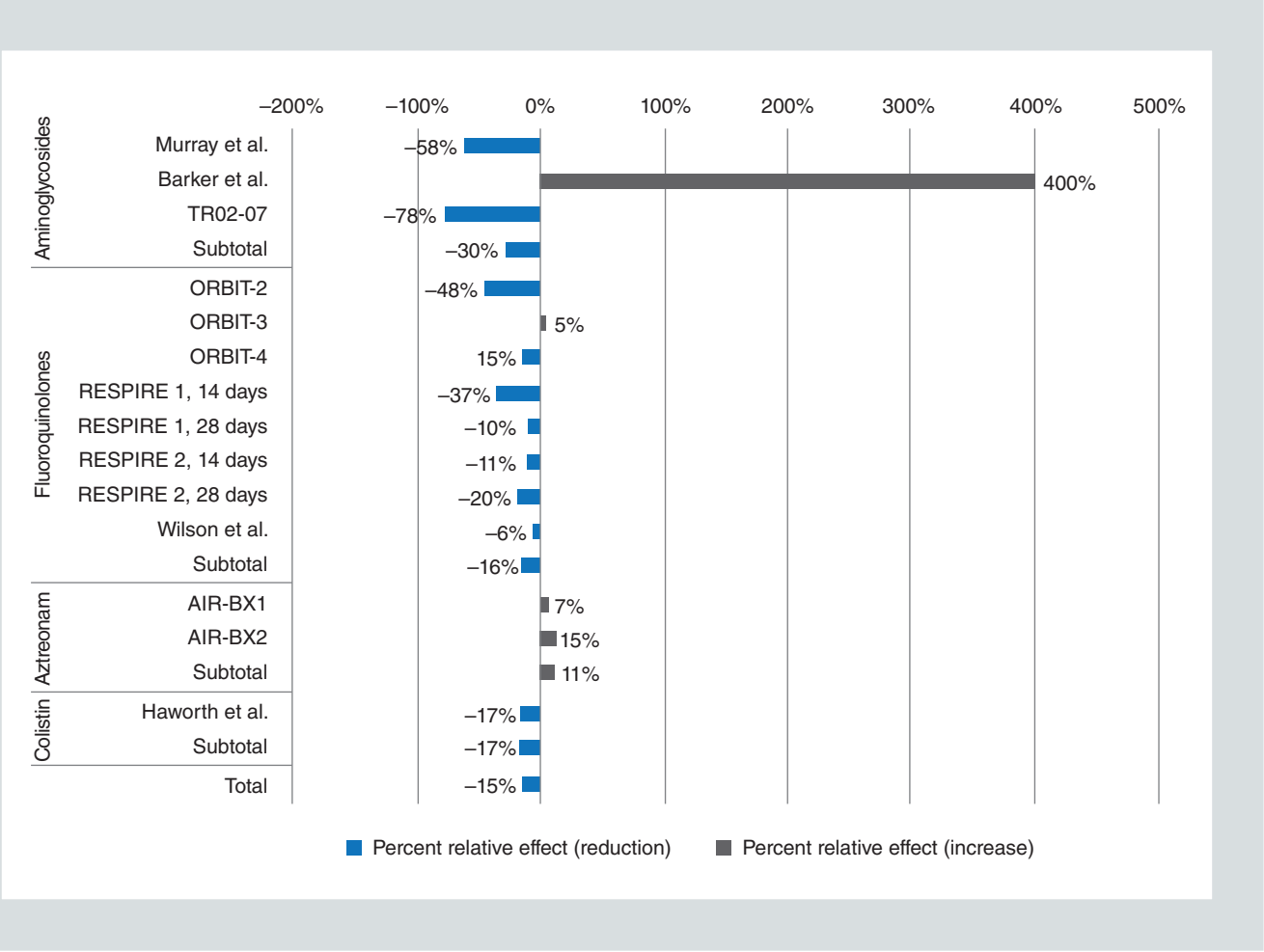

Figure 2. Relative effect of long-term inhaled antibiotics on exacerbation frequency (at least one exacerbation). Data extracted from the meta-analysis of Laska IF et al.[51]

Study (BLESS)[55] showed a significant reduction in exacerbation frequency. None of them required a specific bacterial pathogen to be present at baseline, and in the three trials only 10-29% of patients were chronically infected with *P. aeruginosa*[53-55]. Therefore, society guidelines recommend long-term macrolides as the first option in frequent exacerbators without *P. aeruginosa* infection[1,12]. A recent systematic review and individual patient data meta-analysis provided the first subpopulation analysis and suggested that long-term macrolide therapy is highly effective in reducing the frequency of exacerbations (adjusted incidence rate ratio = 0.49; 95% CI, 0.36 – 0.66; p < 0.0001), (Fig. 3). It concluded that macrolides should be considered in all frequent exacerbators, including those who are infected with *P. aeruginosa*, where the rate ratio was 0.36 (95% CI 0.18 - 0.72; p < 0,004) indicating an even greater benefit than in the general bronchiectasis population[56]. Macrolides should therefore be considered an effective option for patients with *P. aeruginosa* infection. The dose of macrolide used is a subject of considerable debate. The two trials of azithromycin used 500 mg three times per week (EMBRACE) or 250 mg daily (BAT) and

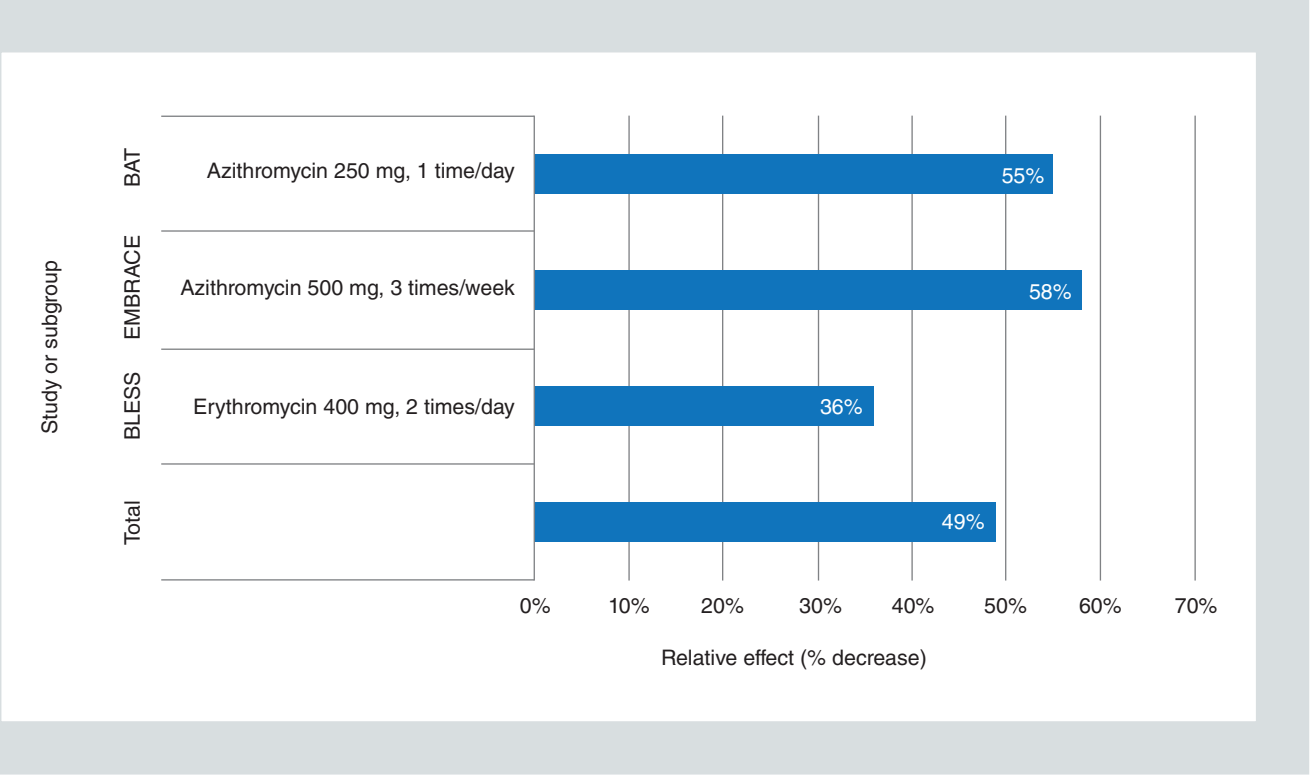

Figure 3. Relative effect of long-term macrolides on exacerbation frequency. Data extracted from the two-step meta-analysis of Chalmers JD et al.[56]

showed a larger effect size than the BLESS trial of erythromycin. The lack of a clear difference in efficacy between EMBRACE and BAT is interesting because BAT utilized a slightly higher dose, and this was associated with a higher rate of gastrointestinal (GI) complications (40% in BAT, but infrequent in EMBRACE). This suggests that intermittent dosing may be associated with similar efficacy but fewer adverse effects (Fig. 3). For this reason, the authors' practice is to use azithromycin 250 mg three times per week, while acknowledging this approach is a lower dose than those tested in the trials.

Alongside their antimicrobial effects, macrolides have been associated with other anti-inflammatory properties in different airway diseases[57]. A recent study by Keir et al.[58] demonstrated that neutrophil extracellular traps (NETs), a method of host defence against pathogens implicated in multiple inflammatory diseases, were abundant in sputum from bronchiectasis patients, and the use of macrolides significantly reduced the concentration of NETs in the sputum of patients with bronchiectasis and *P. aeruginosa* infection. This study supports a novel immunomodulatory effect, allowing a better understanding of how macrolides, which do not have conventional anti-pseudomonal activity, might reduce exacerbations in patients with chronic *P. aeruginosa* infection[58].

Presently, ERS guidelines recommend first option long-term macrolide use in patients with three or more exacerbations, with any

infection other than *P. aeruginosa,* although they can also be used for the treatment of *P. aeruginosa* when there is intolerance of inhaled antibiotics, or in addition to inhaled antibiotics in more severe cases[1].

Nonetheless, the downsides of long-term macrolide treatment must also be taken into account. Patients should be advised of gastrointestinal upset, hearing and balance disturbance and cardiac effects[12,59]. An electrocardiogram to assess QT interval and sputum culture for NTM exclusion should be performed prior to initiation of macrolide therapy[1,12]. Macrolides should be avoided in patients with a prolonged QT interval[7].

A better understanding of the impact of long-term antibiotics on microbial resistance is a research priority[60].

Inhaled corticosteroids and bronchodilators

Inhaled corticosteroids and bronchodilators are widely used due to the overlap of bronchiectasis and other airway chronic diseases. The ERS guidelines recommend inhaled therapies according to standard guidelines for COPD and asthma[1]. In patients with "pure" bronchiectasis, there is much less evidence to guide the use of inhaled therapies. Recent data suggests that bronchiectasis patients with high eosinophil counts may be more responsive to inhaled steroids[61]. Aliberti et al.[62] found symptomatic improvement with inhaled fluticasone treatment, but only when they had blood eosinophilia. There is no role for oral corticosteroids in bronchiectasis without other specific indications, such as ABPA, severe asthma or acute exacerbation of asthma.

Spirometry alone does not encompass the variety of pathophysiological features in bronchiectasis, with some patients presenting air trapping or hyperinflation. So, it is reasonable to treat patients with significant breathlessness with long-acting bronchodilators even in the absence of airflow obstruction on spirometry[1,12,63]. It is suggested to use bronchodilators before ACT, inhaled mucoactive drugs and inhaled antibiotics in order to increase tolerability and optimise pulmonary deposition.

COMPLICATIONS

Treatment should be oriented following individual guidelines for each case. If there is ongoing haemoptysis, the respiratory physiotherapist must review and determine the optimum ACT[12].

Nowadays, surgical intervention is rarely considered in bronchiectasis and reserved for disease that cannot be controlled with medical therapy, or in particular circumstances, such as massive haemoptysis refractory to bronchial artery embolization or difficult-to-treat NTM infection[1,11,12].

There are limited long-term outcome data for bronchiectasis patients after surgery[64] and no randomised controlled trial of surgical treatment versus standard care[1], thus individual risk-benefit assessment should be performed. Lung transplantation could be considered in patients aged 65 years or less, if the FEV_1 is < 30% with significant instability or rapid respiratory deterioration. Close collaboration with

thoracic surgeons and a transplant centre is important to identify patients eligible for transplantation[12].

EXACERBATIONS

Pulmonary exacerbations are key events in the natural history of bronchiectasis, leading to increased airway and systemic inflammation, and accelerating lung damage and FEV_1 decline[65]. In fact, the strongest predictor of future events is a history of frequent exacerbations. Furthermore, chronic infection with *P. aeruginosa* and *H. influenzae*, worse lung function and low BMI were associated with increased exacerbation risk[16,26]. Microbiome studies confirm that *P. aeruginosa* and *H. influenzae* dominated microbiomes were linked to severe disease and frequent exacerbations, despite a marked stability when comparing patients at exacerbation and stable state[20,21]. Prompt antibiotic treatment is the mainstay of treatment for exacerbations, although the proportion of events that are truly caused by bacteria is unknown[66]. Moreover, respiratory viruses can be identified during exacerbations in up to 50% of cases[67]. A sputum sample for bacterial culture should be sent during periods of stability and at exacerbation. Before starting antibiotics, it is recommended to review the previous sputum microbiology and antimicrobial susceptibility to guide antibiotic choice[1,12,24].

Current guidelines recommend a 14-day duration antibiotic course despite the lack of any direct data comparing longer and shorter courses[1,12]. A prospective cohort study including 32 exacerbations treated with 14 days of intravenous antibiotics demonstrated significant improvement in 24h sputum volume, bacterial clearance, C-reactive protein, incremental walk test and St. George's Respiratory Questionnaire (SGRQ), but no improvement in spirometry[68]. A recent randomised trial aimed to assess whether it is feasible, based on bacterial load, to shorten courses of intravenous antibiotics during exacerbations. The study found that shorter courses were superior in terms of time to next exacerbations. This study has important limitations and involved a severe population that may not be fully generalizable[69]. Nevertheless, it is likely that some patients do not require prolonged antibiotic treatment at exacerbation. The ERS guidelines recognised the possibility that mild exacerbations can be treated with shorter courses of antibiotics, like those associated with pathogens more sensitive to antibiotics (e.g. *Streptococcus pneumoniae*) or patients with a rapid return to baseline[1]. On the other hand, patients who present significantly unwell should be considered for admission to the hospital and intravenous antibiotic therapy.

BRONCHIECTASIS AND COVID-19

The COVID-19 pandemic has presented further challenges. Bronchiectasis diagnosis was potentially delayed during this period and its management became more demanding, with reduced face-to-face appointments, fewer sputum samples to guide treatments, cancellation or harder access to PR and ACT classes, sedentarism and anxiety.

However, a small recent observational study showed that bronchiectasis exacerbation frequency was markedly reduced during the first 12 months of the pandemic, without changes in chronic respiratory symptoms. The lockdown

and social distance measures, leading to a reduction in circulating viruses, are the most likely explanations for this exacerbation reduction. This study supports an important role for external environmental factors in bronchiectasis exacerbations[70].

Although these were challenging times, they have also helped to raise important questions about how hygiene and environmental control measures might be used to reduce exacerbations in the future.

NEW PERSPECTIVES

Personalised medicine

Bronchiectasis is a heterogeneous diagnosis incorporating multiple patient subgroups (phenotypes) and molecular entities (endotypes). A one-size-fits-all approach is unlikely to be successful and the optimal population to benefit from antibiotic, mucoactive and anti-inflammatory drugs has yet to be identified.

Biomarkers that could improve risk stratification or therapeutic decision making are needed. As stated above, neutrophil elastase activity in sputum can identify patients at higher risk of airway infection and exacerbations and has been validated as a biomarker across multiple studies. A simple point-of-care semi-quantitative neutrophil elastase assay (NEATstik®) has proven to be useful in identifying bronchiectasis patients with airway infection and at high risk of exacerbation over subsequent 12 months[71]. A recent *post-hoc* analysis of the ORBIT-4 trial has revealed that a higher neutrophil elastase score at baseline, measured through NEATstik®, could predict a better response to inhaled ciprofloxacin[72]. Bacterial load may be also a useful biomarker of disease severity and antibiotics response. Sibila et al.[73] demonstrated, in a *post hoc* analysis of a randomised trial of inhaled aztreonam, a better response to inhaled antibiotics with a higher bacterial load. These two observations are clearly linked, since higher bacterial loads are associated with increased inflammation. Therefore, a concept is emerging whereby we understand that a high bacterial load increases inflammation, which causes worse symptoms. Reducing bacterial load, reduces inflammation and in term reduces mucus production and sputum purulence thereby improving quality of life and preventing exacerbations. There are still, however, relatively few validated biomarkers of treatment response in bronchiectasis and further endotypes are likely to be identified. The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) - Bronchiectasis Research Involving Databases, Genomics and Endotyping to match the right treatment to the right patient (BRIDGE) study is currently taking place intending to identify patient endotypes for a better stratified medicine (NCT03791086).

Expanded future therapies

Despite increased research output over the past 10 years, there is still no licensed therapy in bronchiectasis. Airway inflammation in bronchiectasis is dominated by neutrophils, so much of the development of new treatments has been focused on targeting the neutrophil. Previous studies with neutrophil elastase inhibitors

and CXCR2 antagonists failed to show clinical benefits[74-76].

In a recent trial, Brensocatib, an oral reversible inhibitor of dipeptidyl peptidase 1 (DPP-1), an enzyme responsible for the activation of neutrophil serine proteases such as neutrophil elastase, was studied in bronchiectasis patients with a history of exacerbations[77]. Brensocatib prolonged the time to first exacerbation and led to a lower frequency of exacerbations than placebo, showing the potential clinical benefits of reducing neutrophilic inflammation directly. Further larger and longer-term trials to investigate this therapy are currently underway (NCT04594369).

On the other hand, 20% of bronchiectasis patients present an eosinophilic inflammatory pattern that could be better suppressed through inhaled corticosteroids or anti-eosinophilic therapies[61,62]. Efficacy and safety of benralizumab in patients with non-cystic fibrosis bronchiectasis (MAHALE) is a phase 3 study that is currently recruiting patients to assess the response of Benralizumab in bronchiectasis patients with eosinophilic inflammation (NCT05006573). Therefore, reducing the inflammation might be the ultimate goal of bronchiectasis treatment, avoiding exacerbations and reducing antibiotic exposure.

There is mixed evidence for the role of cystic fibrosis transmembrane conductance regulator (CFTR) mutations in idiopathic bronchiectasis, with some studies reporting that up to 50% of patients with idiopathic bronchiectasis harbour CFTR mutations, which is higher than in the general population. Further studies are needed to fully understand if CFTR modulators will benefit this patient population[78].

CONCLUSIONS

The profile of bronchiectasis has improved over the past 10 years due to a global recognition of its importance and impact on healthcare systems. This is paralleled by increases in the quantity and quality of research in the field. EMBARC published research priorities in 2017 that highlighted a combination of translational and clinical issues, many of which have now been addressed thanks to the rapid expansion of bronchiectasis research[60]. Further studies are needed to move the bronchiectasis treatment towards an endophenotypic precision medicine approach.

Meanwhile, there is a need to provide proper guidance to clinicians. The authors suggest that for clinicians who are not specialised in bronchiectasis care, the priority is "getting the basics right". Current guidelines agree that underlying causes and comorbidities should be addressed, patients should learn ACT and be involved in PR programs or daily exercise, and in some selected cases should be offered long-term antibiotics. Implementation of these key interventions universally would represent a major advance in the management of patients with bronchiectasis.

DISCLOSURES

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REFERENCES

1. Polverino E, Goeminne PC, McDonnell MJ et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017;50: 1700629.
2. British Thoracic Society Bronchiectasis (non-CF) Guideline Group. Guideline for non-cystic fibrosis bronchiectasis. Thorax. 2010;65:1-64.
3. Quint JK, Millett ERC, Joshi M et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: A population-based cohort study. Eur Respir J. 2016;47:186-93.
4. Finklea JD, Khan G, Thomas S, Song J, Myers D, Arroliga AC. Predictors of mortality in hospitalized patients with acute exacerbation of bronchiectasis. Respir Med. 2010;104:816-21.
5. Seitz AE, Olivier KN, Steiner CA, De Oca RM, Holland SM, Prevots DR. Trends and burden of bronchiectasis-associated hospitalizations in the United States, 1993-2006. Chest. 2010;138:944-9.
6. Cole PJ. Inflammation: a two-edged sword--the model of bronchiectasis. Eur J Respir Dis Suppl. 1986;147:6-15.
7. Chalmers JD, Aliberti S, Blasi F. Management of bronchiectasis in adults. Eur Respir J. 2015;45:1446-62.
8. Abo-Leyah H, Chalmers JD. Managing and preventing exacerbation of bronchiectasis. Curr Opin Infect Dis. 2020;33:189-96.
9. Chalmers JD, Chotirmall SH. Bronchiectasis: new therapies and new perspectives. Lancet Respir Med. 2018;6:715-26.
10 Boaventura R, Sibila O, Agusti A, Chalmers JD. Treatable traits in bronchiectasis. Eur Respir J. 2018;52:1-6.
11. Palange P, Rohde G (Eds.). ERS HANDBOOK Respiratory Medicine 3rd Edition. 2019.
12. Hill AT, Sullivan AL, Chalmers JD et al. British Thoracic Society Guideline for bronchiectasis in adults. Thorax. 2019;74(Suppl. 1):1-69.
13. Altenburg J, Goeminne P. Defining severe bronchiectasis. Eur Respir Monogr. 2018;81:62-81.
14. Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2012; 186:657-65.
15. Boaventura R, Shoemark A, Chalmers JA. Pathophysiology. Eur Respir Monogr. 2018; 81: 8-28.
16. Araújo D, Shteinberg M, Aliberti S et al. The independent contribution of Pseudomonas aeruginosa infection to long-term clinical outcomes in bronchiectasis. Eur Respir J. 2018;51: 1701953.
17. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. Ann Am Thorac Soc. 2015;12:1602-11.
18. Fowler SJ, French J, Screaton NJ et al. Nontuberculous mycobacteria in bronchiectasis: Prevalence and patient characteristics. Eur Respir J. 2006;28: 1204-10.
19. Mirsaeidi M, Farnia P, Sadikot R, Hsueh P-R, Aliberti S. Nontuberculous Mycobacteria: Epidemiologic, Mycobacteriologic, and Clinical Aspects. Biomed Res Int. 2015;2015:523697.
20. Richardson H, Dicker AJ, Barclay H, Chalmers JD. The microbiome in bronchiectasis. Eur Respir Rev. 2019;28:190048.
21. Dicker AJ, Lonergan M, Keir HR et al. The sputum microbiome and clinical outcomes in patients with bronchiectasis: a prospective observational study. Lancet Respir Med. 2021;9:885-96.
22. Chalmers JD. Phenotypes and endotypes. Eur Respir Monogr 2018;81: 133-52.
23. Araújo D, Shteinberg M, Aliberti S et al. Standardised classification of the aetiology of bronchiectasis using an objective algorithm. Eur Respir J. 2017; 50:3-6.
24. Martínez-García MÁ, Máiz L, Olveira C et al. Spanish Guidelines on the Evaluation and Diagnosis of Bronchiectasis in Adults. Arch Bronconeumol. 2018;54:79-87.
25. Dente FL, Roggi MA, Del Cesta R, Polverino E, Paggiaro P. Eur Respir Monogr. 2018;81:167-85.
26. Chalmers JD, Goeminne P, Aliberti S et al. The bronchiectasis severity index an international derivation and validation study. Am J Respir Crit Care Med. 2014;189:576-85.
27. Martínez-García MA, De Gracia J, Relat MV et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: The FACED score. Eur Respir J. 2014;43:1357-67.
28. Martinez-Garcia MA, Athanazio RA, Girón R et al. Predicting high risk of exacerbations in bronchiectasis: The E-FACED score. Int J COPD. 2017;12:275-84.
29. Chalmers JD, Moffitt KL, Suarez-Cuartin G et al. Neutrophil elastase activity is associated with exacerbations and lung function decline in bronchiectasis. Am J Respir Crit Care Med. 2017;195:1384-93.
30. O'Neill K, O'Donnell AE, Bradley JM. Airway clearance, mucoactive therapies and pulmonary rehabilitation in bronchiectasis. Respirology. 2019;24:227–37.
31. Lee AL, Burge AT, Holland AE. Airway clearance techniques for bronchiectasis. Cochrane Database Syst Rev. 2015. 2015;:CD008351.
32. Muñoz G, de Gracia J, Buxó M, Alvarez A, Vendrell M. Long-term benefits of airway clearance in bronchiectasis: a randomised placebo-controlled trial. Eur Respir J. 2018;51:1701926.
33. Ong HK, Lee AL, Hill CJ, Holland AE, Denehy L. Effects of pulmonary rehabilitation in bronchiectasis: A retrospective study. Chron Respir Dis. 2011;8: 21-30.
34. Patel S, Cole AD, Nolan CM et al. Pulmonary rehabilitation in bronchiectasis: a propensity-matched study. Eur Respir J. 2019;53:801264.
35. Lee AL, Hill CJ, McDonald CF, Holland AE. Pulmonary Rehabilitation in Individuals With Non-Cystic Fibrosis Bronchiectasis: A Systematic Review. Arch Phys Med Rehabil. 2017;98:774-78.
36. Alcaraz-Serrano V, Gimeno-Santos E, Scioscia G et al. Association between physical activity and risk of hospitalisation in bronchiectasis. Eur Respir J. 2020;55:1902138.
37. Bilton D, Tino G, Barker AF et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax. 2014;69:1073-9.
38. Bilton D, Daviskas E, Anderson SD et al. Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-cystic fibrosis bronchiectasis. Chest. 2013;144:215-25.
39. Gao Y-H, Abo Leyah H, Finch S et al. Relationship between Symptoms, Exacerbations, and Treatment Response in Bronchiectasis. Am J Respir Crit Care Med. 2020;201:1499-1507.
40. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. rhDNase Study Group. Chest. 1998;113:1329-34.
41. Qi Q, Ailiyaer Y, Liu R et al. Effect of N-acetylcysteine on exacerbations of bronchiectasis (BENE): a randomized controlled trial. Respir Res. 2019;20:73.
42. Vallières E, Tumelty K, Tunney MM et al. Efficacy of Pseudomonas aeruginosa eradication regimens in bronchiectasis. Eur Respir J. 2017;49:1600851.
43. Pieters A, Bakker M, Hoek RAS et al. The clinical impact of Pseudomonas aeruginosa eradication in bronchiectasis in a Dutch referral centre. Eur Respir J. 2019;53:1802081.
44. Aliberti S, Goeminne PC, O'Donnell AE et al. Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. Lancet Respir Med. 2021;S2213-2600(21)00277-0.
45. Quon BS, Goss CH, Ramsey BW. Inhaled antibiotics for lower airway infections. Ann Am Thorac Soc. 2014;11:425-34.
46. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. Am J Respir Crit Care Med. 2014;189:975-82.
47. Haworth C, Shteinberg M, Winthrop K et al. The efficacy and safety of colistimethate sodium delivered via the Ineb in bronchiectasis: the PROMIS-I randomized controlled trial, ERJ. 2021;58(Suppl. 65): RCT4267.
48. De Soyza A, Aksamit T, Bandel TJ et al. Respire 1: A phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J. 2018;51:1702052.

49. Aksamit T, De Soyza A, Bandel T-J et al. RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J. 2018;51:1702053.
50. Haworth CS, Bilton D, Chalmers JD et al. Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with Pseudomonas aeruginosa (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials. Lancet Respir Med. 2019;7:213-26.
51. Laska IF, Crichton ML, Shoemark A, Chalmers JD. The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis. Lancet Respir Med. 2019;7:855-69.
52. Chalmers JD, Cipolla D, Thompson B et al. Changes in respiratory symptoms during 48-week treatment with ARD-3150 (inhaled liposomal ciprofloxacin) in bronchiectasis: results from the ORBIT-3 and -4 studies. Eur Respir J. 2020;56:2000110.
53. Wong C, Jayaram L, Karalus N et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet. 2012;380:660-7.
54. Altenburg J, de Graaff CS, Stienstra Y et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA. 2013;309:1251-9.
55. Serisier DJ, Martin ML, McGuckin MA et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA. 2013; 309:1260-7.
56. Chalmers JD, Boersma W, Lonergan M et al. Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis. Lancet Respir Med. 2019;7:845-54.
57. Kanoh S, Rubin BK. Mechanisms of action and clinical application of macrolides as immunomodulatory medications. Clin Microbiol Rev. 2010;23:590-615.
58. Keir HR, Shoemark A, Dicker AJ et al. Neutrophil extracellular traps, disease severity, and antibiotic response in bronchiectasis: an international, observational, multicohort study. Lancet Respir Med. 2021;9:873-84.
59. Smith D, Du Rand I, Addy CL et al. British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease. Thorax. 2020;75:370-404.
60. Aliberti S, Masefield S, Polverino E et al. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. Eur Respir J. 2016;48:632-47.
61. Polverino E, Dimakou K, Hurst J et al. The overlap between bronchiectasis and chronic airway diseases: state of the art and future directions. Eur Respir J. 2018;52:1800328.
62. Aliberti S, Sotgiu G, Blasi F, Saderi L, Posadas T, Martinez Garcia MA. Blood eosinophils predict inhaled fluticasone response in bronchiectasis. Eur Respir J. 2020;56:2000453.
63. Radovanovic D, Santus P, Blasi F et al. A comprehensive approach to lung function in bronchiectasis. Respir Med. 2018;145:120-9.
64. Zhang P, Zhang F, Jiang S et al. Video-assisted thoracic surgery for bronchiectasis. Ann Thorac Surg. 2011;91:239-43.
65. de la Rosa D, Martínez-Garcia M-A, Olveira C, Girón R, Máiz L, Prados C. Annual direct medical costs of bronchiectasis treatment: Impact of severity, exacerbations, chronic bronchial colonization and chronic obstructive pulmonary disease coexistence. Chron Respir Dis. 2016;13:361-71.
66. Mendes MA, Shoemark A, Chalmers JD. Bronchiectasis Exacerbations: Clinical relevance and Management. BRN Rev. 2018;4:169-184.
67. Gao Y-H, Guan W-J, Xu G et al. The role of viral infection in pulmonary exacerbations of bronchiectasis in adults: a prospective study. Chest. 2015; 147:1635-43.
68. Murray MP, Turnbull K, Macquarrie S, Hill AT. Assessing response to treatment of exacerbations of bronchiectasis in adults. Eur Respir J. 2009;33:312-8.
69. Bedi P, Cartlidge MK, Zhang Y et al. Feasibility of shortening intravenous antibiotic therapy based on bacterial load- a proof of concept randomised controlled trial. Eur Respir J. 2021;58:2004388.
70. Crichton ML, Shoemark A, Chalmers JD. The Impact of the COVID-19 Pandemic on Exacerbations and Symptoms in Bronchiectasis: A Prospective Study. Am J Respir Crit Care Med. 2021;204:857-9.
71. Shoemark A, Cant E, Carreto L et al. A point-of-care neutrophil elastase activity assay identifies bronchiectasis severity, airway infection and risk of exacerbation. Eur Respir J. 2019;53:1900303.
72. Abo-Leyah H, Richardson H, Pembridge T et al. Sputum neutrophil elastase and inhaled antibiotic response in bronchiectasis: a post-hoc analysis of the ORBIT-4 trial. ERJ. 2021;58(Suppl. 65):OA1310.
73. Sibila O, Laserna E, Shoemark A et al. Airway bacterial load and inhaled antibiotic response in bronchiectasis. Am J Respir Crit Care Med. 2019;200: 33-41.
74. Stockley R, De Soyza A, Gunawardena K et al. Phase II study of a neutrophil elastase inhibitor (AZD9668) in patients with bronchiectasis. Respir Med. 2013;107:524-33.
75. Watz H, Nagelschmitz J, Kirsten A et al. Safety and efficacy of the human neutrophil elastase inhibitor BAY 85-8501 for the treatment of non-cystic fibrosis bronchiectasis: A randomized controlled trial. Pulm Pharmacol Ther. 2019;56:86-93.
76. De Soyza A, Pavord I, Elborn JS et al. A randomised, placebo-controlled study of the CXCR2 antagonist AZD5069 in bronchiectasis. Eur Respir J. 2015;46:1021-32.
77. Chalmers JD, Haworth CS, Metersky ML et al. Phase 2 Trial of the DPP-1 Inhibitor Brensocatib in Bronchiectasis. N Engl J Med. 2020;383:2127-37.
78. Patel SD, Bono TR, Rowe SM, Solomon GM. CFTR targeted therapies: recent advances in cystic fibrosis and possibilities in other diseases of the airways. Eur Respir Rev. 2020;29:190068.