Exacerbation of Bronchiectasis

15

Eva Polverino, Edmundo Rosales-Mayor, and Antoni Torres

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.

E. Polverino (✉)
Institut de Recerca Vall d'Hebron (VHIR), Servei de Pneumologia, Hospital Universitari Vall d'Hebron (HUVH), Barcelona 08035, Spain
e-mail: eva.polverino@vhir.org

E. Rosales-Mayor
Servicio de Neumología, Hospital General de Catalunya, Sant Cugat–Hospital El Pilar, Barcelona, Spain

Fundaciò Clìnic, Barcelona, Spain

A. Torres
Department of Pneumology, Institut Clínic Respiratori, Hospital Clinic of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), University of Barcelona, Ciber de Enfermedades Respiratorias (CIBERES), Barcelona, Spain
e-mail: atorres@clinic.ub.es

J. Chalmers et al. (eds.), *Bronchiectasis*,
https://doi.org/10.1007/978-3-319-61452-6_15

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.

References

1. 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(7):657–65.
2. Sheehan RE, Wells AU, Copley SJ, et al. A comparison of serial computed tomography and functional change in bronchiectasis. Eur Respir J. 2002;20(3):581–7.
3. 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(5):576–85.
4. Aliberti S, Lonni S, Dore S, et al. Clinical phenotypes in adult patients with bronchiectasis. Eur Respir J. 2016;47(4):1113–22.

5. Kapur N, Masters IB, Chang AB. Longitudinal growth and lung function in pediatric non-cystic fibrosis bronchiectasis: what influences lung function stability? Chest. 2010;138(1):158–64.
6. 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(5):1357–67.
7. Martinez-Garcia MA, Athanazio RA, Girón RM, et al. Predicting high risk of exacerbations in bronchiectasis: the E-FACED score. Int J Chron Obstruct Pulmon Dis. 2017;12:275–84. https://doi.org/10.2147/COPD.S121943.
8. Rosales-Mayor E, Polverino E, Raguer L, Alcaraz V, Garrabus A, Ranzani O, Menendez R, Torres A. Comparison of two prognostic scores (BSI and FACED) in a Spanish cohort of adult patients with bronchiectasis and improvement of the FACED predictive capacity for exacerbations. PLoS One. 2017;12(4):e0175171.
9. Pasteur MC, Bilton D, Hill AT, et al. BTS guideline for non-CF bronchiectasis. Thorax. 2010;65(Suppl 1):1–58.
10. Vendrell M, Gracia J, de Olveira C, et al. Normativa SEPAR: diagnóstico y tratamiento de las bronquiectasias. Arch Bronconeumol. 2008;44(11):629–40.
11. Altenburg J. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis. JAMA. 2013;309(12):1251–9.
12. 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(9842):660–7.
13. 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(12):1260–7.
14. Serisier DJ, Bilton D, De Soyza A, et al. Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis (ORBIT-2): a randomised, double-blind, placebo-controlled trial. Thorax. 2013;68(9):812–7.
15. Wilson R, Welte T, Polverino E, et al. Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study. Eur Respir J. 2013;41(5):1107–15.
16. Polverino et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017;50(3). pii: 1700629.
17. Bilton D, Daviskas E, Anderson D, 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(1):215.
18. Bilton D, Tino G, Barker AF, et al. Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax. 2014;69(12):1073–9.
19. Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med. 2011;105(12):1831–5.
20. Mandal P, Chalmers JD, Graham C, et al. Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial. Lancet Respir Med. 2014;2(6):455–63.
21. Hernando R, Drobnic ME, Cruz MJ, et al. Budesonide efficacy and safety in patients with bronchiectasis not due to cystic fibrosis. Int J Clin Pharm. 2012;34(4):644–50.
22. Lee AL, Hill CJ, Cecins N, et al. The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis—a randomised controlled trial. Respir Res. 2014;15(1):44.
23. Barker AF, O'Donnell AE, Flume P, et al. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. Lancet Respir Med. 2014;2(9):738–49.
24. Martínez-García MÁ, Soler-Cataluña JJ, Catalán-Serra P, Román-Sánchez P, PerpiñáTordera M. Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. Chest. 2012;141(2):461–8.
25. Murray MP, Pentland JL, Hill AT. A randomised crossover trial of chest physiotherapy in non-cystic fibrosis bronchiectasis. Eur Respir J. 2009;34(5):1086–92.
26. Nicolson CHH, Stirling RG, Borg BM, Button BM, Wilson JW, Holland AE. The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med. 2012;106(5):661–7.

27. 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(8):975–82.
28. Bilton D, Henig N, Morrissey B, Gotfried M. Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of Pseudomonas Aeruginosa infection in adult bronchiectasis. Chest. 2006;130(5):1503–10.
29. Kapur N, Masters IB, Morris PS, Galligan J, Ware R, Chang AB. Defining pulmonary exacerbation in children with non-cystic fibrosis bronchiectasis. Pediatr Pulmonol. 2012;47(1): 68–75.
30. Valery PC, Morris PS, Byrnes CA, et al. Long-term azithromycin for indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis intervention study): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med. 2013;1(8):610–20.
31. Patterson JE, Hewitt O, Kent L, Bradbury I, Elborn JS, Bradley JM. Acapella versus "usual airway clearance" during acute exacerbation in bronchiectasis: a randomized crossover trial. Chron Respir Dis. 2007;4(2):67–74.
32. Murphy MK, Black NA, Lamping DL, et al. Consensus development methods, and their use in clinical guideline development. Health Technol Assess. 1998;2(3):i–iv. 1–88
33. Chan TH, Ho SS, Lai CK, et al. Comparison of oral ciprofloxacin and amoxycillin in treating infective exacerbations of bronchiectasis in Hong Kong. Chemotherapy. 1996;42(2):150–6.
34. Currie DC, Garbett ND, Chan KL, et al. Double blind randomized study of prolonged higher-dose oral amoxycillin in purulent bronchiectasis. QJM. 1990;76(2):799–816.
35. Currie DC, Munro C, Gaskell D, Cole PJ. Practice, problems and compliance with postural drainage: a survey of chronic sputum producers. Br J Dis Chest. 1986;80(C):249–53.
36. Lam WK, Chau PY, So SY, et al. Ofloxacin compared with amoxycillin in treating infective exacerbations in bronchiectasis. Respir Med. 1989;83(4):299–303.
37. Tsang KWT, Ho PI, Chan KN, et al. A pilot study of low-dose erythromycin in bronchiectasis. Eur Respir J. 1999;13(2):361–4.
38. Wilson CB, Jones PW, O'Leary CJ, Hansell DM, Cole PJ, Wilson R. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. Eur Respir J. 1997;10(8):1754–60.
39. Chalmers JD, Aliberti S, Polverino E, et al. The EMBARC European bronchiectasis registry: protocol for an international observational study. ERJ Open Res. 2016;2(1):81-2015.
40. Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and economic burden of bronchiectasis. Clin Pulm Med. 2005;12(4):205–9.
41. Ringshausen FC, de Roux A, Pletz MW, Hämäläinen N, Welte T, Rademacher J. Bronchiectasis-associated hospitalizations in Germany, 2005-2011: a population-based study of disease burden and trends. PLoS One. 2013;8(8):e71109.
42. Bibby S, Milne R, Beasley R. Hospital admissions for non-cystic fibrosis bronchiectasis in New Zealand. N Z Med J. 2015;128(1421):30–8.
43. UK D of HN. Hospital Episode Statistics 2002–2003. Dep Heal NHLBI UK; 2004.
44. 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(4):944–9.
45. de la Rosa D, Martinez-Garcia M-A, Olveira C, Giron R, Maiz 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(4):361–71.
46. 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(6):816–21.
47. Goeminne PC, Nawrot TS, Ruttens D, Seys S, Dupont LJ. Mortality in non-cystic fibrosis bronchiectasis: a prospective cohort analysis. Respir Med. 2014;108(2):287–96.
48. Kadowaki T, Yano S, Wakabayashi K, et al. An analysis of etiology, causal pathogens, imaging patterns, and treatment of Japanese patients with bronchiectasis. Respir Investig. 2015;53(1):37–44.

49. McDonnell MJ, Jary HR, Perry A, et al. Non cystic fibrosis bronchiectasis: a longitudinal retrospective observational cohort study of pseudomonas persistence and resistance. Respir Med. 2015;109(6):716–26.
50. 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(11):1602–11.
51. Loebinger MR, Wells AU, Hansell DM, et al. Mortality in bronchiectasis: a long-term study assessing the factors influencing survival. Eur Respir J. 2009;34(4):843–9.
52. Rogers GB, Zain NMM, Bruce KD, et al. A novel microbiota stratification system predicts future exacerbations in bronchiectasis. Ann Am Thorac Soc. 2014;11(4):496–503.
53. Li J, Jiao R, Wen LF, Du XB, Gao Y, Li XY, Chen Y, Wu YXLS. The derivation and validation of a scoring system for identifying patients with bronchiectasis at risk of exacerbations. Zhonghua Jie He He Hu Xi Za Zhi. 2016;39(8):598–602.
54. Mao B, Yang JW, Lu HW, Xu JF. Asthma and bronchiectasis exacerbation. Eur Respir J. 2016;47(6):1680–6.
55. Du Q, Jin J, Liu X, Sun Y. Bronchiectasis as a comorbidity of chronic obstructive pulmonary disease: a systematic review and meta-analysis. PLoS One. 2016;11(3):e0150532.
56. Menzies D, Holmes L, McCumesky G, Prys-Picard C, Niven R. Aspergillus sensitization is associated with airflow limitation and bronchiectasis in severe asthma. Eur J Allerg Clin Immunol. 2011;66(5):679–85.
57. Gupta S, Siddiqui S, Haldar P, et al. Quantitative analysis of high-resolution computed tomography scans in severe asthma subphenotypes. Thorax. 2010;65(9):775 LP–781.
58. Mandal P, Morice AH, Chalmers JD, Hill AT. Symptoms of airway reflux predict exacerbations and quality of life in bronchiectasis. Respir Med. 2013;107(7):1008–13.
59. Failla ML. Trace elements and host defense: recent advances and continuing challenges. J Nutr. 2003;133(5):1443S–7S.
60. Hollander FM, van Pierre DD, de Roos NM, van de Graaf EA, Iestra JA, Westaby D. Effects of nutritional status and dietetic interventions on survival in cystic fibrosis patients before and after lung transplantation. J Cyst Fibros. 2014;13(2):212–8.
61. Qi Q, Li T, Li JC, Li Y. Association of body mass index with disease severity and prognosis in patients with non-cystic fibrosis bronchiectasis. Braz J Med Biol Res. 2015;48(8):715–24.
62. Chalmers JD, McHugh BJ, Docherty C, Govan JRW, Hill AT. Vitamin-D deficiency is associated with chronic bacterial colonisation and disease severity in bronchiectasis. Thorax. 2012;68:39–47.
63. Redding GJ, Singleton RJ, Valery PC, et al. Respiratory exacerbations in indigenous children from two countries with non-cystic fibrosis chronic suppurative lung disease/bronchiectasis. Chest. 2014;146(3):762–74.
64. Roberts ME, Lowndes L, Milne DG, Wong CA. Socioeconomic deprivation, readmissions, mortality and acute exacerbations of bronchiectasis. Intern Med J. 2012;42(6):e129–36.
65. Miravitlles M, Anzueto A, Ewig S, Legnani D, Stauch K. Characterisation of exacerbations of chronic bronchitis and COPD in Europe: the GIANT study. Ther Adv Respir Dis. 2009;3:267–77.
66. Rosales Mayor E, Menendez R, Alcaraz-Serrano V, et al. Pneumonic vs. non-pneumonic exacerbations in bronchiectasis. Eur Respir J. 2016;48(Suppl 60):OA279.
67. Metaxas EI, Balis E, Papaparaskevas J, Spanakis NE, Tatsis G, Tsakris A. Bronchiectasis exacerbations: the role of atypical bacteria and respiratory syncytial virus. Can Respir J. 2015;22(3):163–6.
68. Gao YH, Guan WJ, Xu G, et al. The role of viral infection in pulmonary exacerbations of bronchiectasis in adults: a prospective study. Chest. 2015;147(6):1635–43.
69. Kapur N, Mackay IM, Sloots TP, Masters IB, Chang AB. Respiratory viruses in exacerbations of non-cystic fibrosis bronchiectasis in children. Arch Dis Child. 2014;99(8):749–53.
70. Wat D, Gelder C, Hibbitts S, et al. The role of respiratory viruses in cystic fibrosis. J Cyst Fibros. 2008;7(4):320–8.

71. Wedzicha JA. Role of viruses in exacerbations of chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2012;1(2):115–20.
72. Mallia P, Message SD, Gielen V, et al. Experimental rhinovirus infection as a human model of chronic obstructive pulmonary disease exacerbation. Am J Respir Crit Care Med. 2011;183(6):734–42.
73. Mallia P, Footitt J, Sotero R, et al. Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(11):1117–24.
74. Sethi S, Sethi R, Eschberger K, et al. Airway bacterial concentrations and exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2007;176(4):356–61.
75. Tunney MM, Einarsson GG, Wei L, et al. Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation. Am J Respir Crit Care Med. 2013;187(10):1118–26.
76. Brill SE, Patel ARC, Singh R, Mackay AJ, Brown JS, Hurst JR. Lung function, symptoms and inflammation during exacerbations of non-cystic fibrosis bronchiectasis: a prospective observational cohort study. Respir Res. 2015;16:16.
77. Murray MP, Turnbull K, MacQuarrie S, Hill AT. Assessing response to treatment of exacerbations of bronchiectasis in adults. Eur Respir J. 2009;33(2):312–7.
78. Polverino E, Menendez R, Cilloniz C, et al. Microbial aetiology and outcomes of CAP in bronchiectatic patients. Eur Respir J. 2014;42(Suppl 57):4646.
79. Griffith DE, Aksamit TR. Therapy of refractory nontuberculous mycobacterial lung disease. Curr Opin Infect Dis. 2012;25(2):218–27.
80. PROLONGED antibiotic treatment of severe bronchiectasis; a report by a subcommittee of the antibiotics clinical trials (non-tuberculous) committee of the medical research council. Br Med J. 1957;2(5039):255–9.
81. McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway Pseudomonas Aeruginosa in cystic fibrosis. Am J Respir Crit Care Med. 2008;178(9):921–8.
82. Retsch-Bogart GZ, Quittner AL, Gibson RL, et al. Efficacy and safety of inhaled aztreonam lysine for airway pseudomonas in cystic fibrosis. Chest. 2009;135(5):1223–32.
83. Murray MP, Govan JRW, Doherty CJ, et al. A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med. 2011;183(4):491–9.
84. de Soyza A, Aksamit T, Operschall E, et al. LATE-breaking abstract: baseline demographic profile of subjects of the phase 3 RESPIRE 1 trial of ciprofloxacin dry powder for inhalation (DPI) in non-cystic fibrosis bronchiectasis (NCFB). Eur Respir J. 2015;46(Suppl. 59):PA2617.
85. Alcaraz Serrano V, Herrero Cortina B, Vilaró Casamitjana J, Rosales Mayor E, Torres Martí A, Polverino E. Effects of hypertonic saline on sputum clearance in patients with bronchiectasis. Eur Respir J. 2016;48(Suppl 60):OA4821.
86. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human DNase I. Chest. 1998;113(5):1329–34.
87. Guimarães FS, Moço VJR, Menezes SLS, Dias CM, Salles REB, Lopes AJ. Effects of ELTGOL and flutter VRP1® on the dynamic and static pulmonary volumes and on the secretion clearance of patients with bronchiectasis. Rev Bras Fis. 2012;16(2):108–13.
88. Figueiredo PHS, Zin WA, Guimarães FS. Flutter valve improves respiratory mechanics and sputum production in patients with bronchiectasis. Physiother Res Int. 2012;17(1):12–20.
89. Patterson JE, Bradley JM, Hewitt O, Bradbury I, Elborn JS. Airway clearance in bronchiectasis: a randomized crossover trial of active cycle of breathing techniques versus Acapella®. Respiration. 2005;72(3):239–42.
90. Herrero-Cortina B, Vilar J, Mart D, et al. Short-term effects of three slow expiratory airway clearance techniques in patients with bronchiectasis: a randomised crossover trial. Physiotherapy. 2016;102(4):357–64.
91. Lee AL, Hill CJ, McDonald CF, Holland AE. Pulmonary rehabilitation in individuals with non-cystic fibrosis bronchiectasis: a systematic review. Arch Phys Med Rehabil. 2016;98(4):774–782.e1.

92. Zanini A, Aiello M, Adamo D, et al. Effects of pulmonary rehabilitation in patients with non-cystic fibrosis bronchiectasis: a retrospective analysis of clinical and functional predictors of efficacy. Respiration. 2015;89(6):525–33.
93. Mandal P, Sidhu MK, Kope L, et al. A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis. Respir Med. 2012;106(12):1647–54.
94. Newall C, Stockley RA, Hill SL. Exercise training and inspiratory muscle training in patients with bronchiectasis. Thorax. 2005;60:943–8.
95. Jan van Hoek A, Andrews N, Waight PA, et al. The effect of underlying clinical conditions on the risk of developing invasive pneumococcal disease in England. J Inf Secur. 2012;65(1):17–24.
96. Butler JC, Schuchat A. Epidemiology of pneumococcal infections in the elderly. Drugs Aging. 1999;15(Suppl 1):11–9.
97. Grohskopf LA, Sokolow LZ, Broder KR, et al. Prevention and control of seasonal influenza with vaccines. MMWR Recomm Rep. 2016;65(5):1–54.
98. Jackson LA, Gurtman A, van Cleeff M, et al. Immunogenicity and safety of a 13-valent pneumococcal conjugate vaccine compared to a 23-valent pneumococcal polysaccharide vaccine in pneumococcal vaccine-naive adults. Vaccine. 2013;31(35):3577–84.
99. Guan W-J, Gao Y-H, Xu G, et al. Inflammatory responses, spirometry, and quality of life in subjects with bronchiectasis exacerbations. Respir Care. 2015;60(8):1180–9.