BRN Reviews REVIEW

Bronchiectasis Exacerbations: Clinical Relevance and Management

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ABSTRACT

Bronchiectasis is a clinico-radiological syndrome with variable course. Some patients are stable for years and others develop frequent exacerbations, characterised by symptoms such as increased cough and change in sputum and/or systemic features. Bacterial infections are the most frequent recognised trigger, and consequently the majority of these events are treated with systemic antibiotics. As a major cause of morbidity, mortality and healthcare related costs, exacerbations have been used as primary outcomes in clinical trials of new treatments in bronchiectasis. Furthermore, implementing prevention strategies in patients at risk of future exacerbations is a major goal of bronchiectasis management. However, evidence-based knowledge on bronchiectasis exacerbations is limited and there is no specific licensed-treatment. Further studies using the recently developed consensus-based definition are needed to clarify the unanswered questions regarding the pathophysiology, prevention and treatment of bronchiectasis exacerbations. This review summarises the existing evidence and the gaps in our knowledge of bronchiectasis exacerbations.

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INTRODUCTION

Bronchiectasis is a complex and heterogeneous chronic respiratory disease defined by clinical and radiological criteria. Daily productive cough is the most characteristic symptom and irreversible bronchial dilatation on high resolution computed tomography (HRCT) of the chest confirms the diagnosis[1-4].

The natural course of bronchiectasis is marked by exacerbations, traditionally associated with a new and/or persistent bacterial infection that causes increased inflammation and further lung damage[5]. These events have a significant impact on: 1) patients' short- and long-term experience of the disease, such as daily symptoms and quality of life (QoL); 2) clinical outcomes, such as lung function and survival; and 3) direct and indirect healthcare costs[6-12]. Accordingly, exacerbation frequency and time to first exacerbation have been the most widely used outcomes in clinical trials assessing treatment of bronchiectasis, namely inhaled antibiotics[13-18]. For a chronic disease, the frequency of exacerbations is likely to be the most clinically relevant outcome and is the variable used most often for clinical decision making.

The global prevalence of bronchiectasis is unknown, but studies have suggested that it varies between 52 and 566 cases per 100,000 population. Moreover, there is some evidence that patients experience on average between 1 and 6 exacerbations per year in different populations, and the frequency increases with disease severity[12,19-21]. Bronchiectasis is still believed to be underdiagnosed and so prevalence estimates are likely to increase with time. Based on these facts, prevention and adequate treatment of exacerbations are two major goals of bronchiectasis management in everyday clinical practice and the focus of recent research.

In this review we highlight the research literature on bronchiectasis exacerbations in the context of clinical practice.

DEFINITION OF EXACERBATION

In 2017, a worldwide group of experts led by the European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) and United States (US) Bronchiectasis Registry groups performed a systematic review of exacerbation definitions and organized a Delphi process followed by a round-table meeting to reach a consensus definition (Fig. 1). They defined bronchiectasis exacerbation for research purposes as "a deterioration in ≥ 3 of the following key symptoms for at least 48 hours: cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, haemoptysis AND a clinician determines that a change in bronchiectasis treatment is required"[22]. This symptom-based definition emphasises the importance of an intervention that includes, but is not limited to, institution of antibiotics. Regarding its clinical picture, nonspecific symptoms, such as cough, breathlessness or fatigue, complement features suggestive of bacterial infection (e.g., sputum volume and/or consistency, sputum purulence). As referred by the working group, this definition should be applied in a research context and is not intended to be used in clinical practice[22]. However, clinicians can use

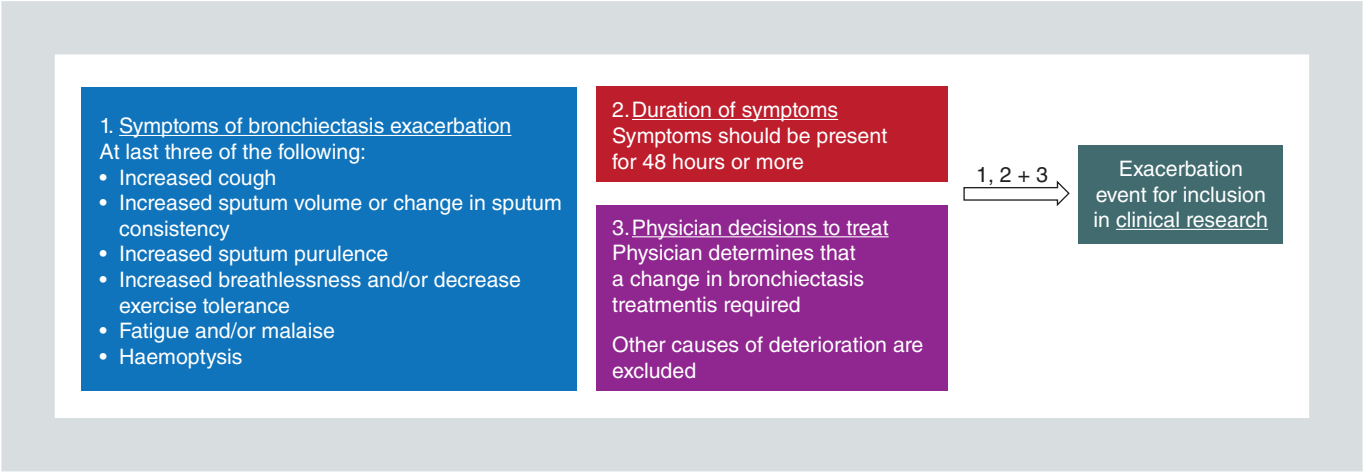

Figure 1. Consensus-based definition of bronchiectasis exacerbation *(adapted and reproduced with permission from Hill AT et al.[22]).*

it in an integrative manner, recognising that no concept of chronic respiratory disease exacerbation is perfect to adopt into routine clinical practice.

In the Spanish guidelines on treatment of bronchiectasis, an exacerbation is defined as "an acute sustained clinical deterioration characterised by an increase in the usual cough and changes in the sputum characteristics consisting of increased purulence, volume or viscosity, which may be accompanied by an increase in dyspnoea, fever, asthenia, poor general condition, anorexia, pleuritic chest pain, haemoptysis, changes in the respiratory examination, changes in the patient's usual treatment or a significant decline in lung function"[23]. The British Thoracic Society (BTS) guideline for non-Cystic Fibrosis (CF) bronchiectasis defined an exacerbation requiring antibiotics as "an acute deterioration with worsening local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness, haemoptysis) and/or systemic upset"[1]. These are broader definitions that do not include the component time or requirement of a minimum number of criteria. It remains speculative which definition is best suited for application in clinical setting.

Depending on the severity of the exacerbation and/or the severity of the underlying disease, these events can be managed in the community or in the hospital. Severity assessment of bronchiectasis exacerbations is not well established. The BTS guideline recommends hospitalisation if the patients are unable to cope at home or if they develop cyanosis or confusion, breathlessness with respiratory rate ≥ 25/min, circulatory or respiratory failure or temperature ≥ 38°C. Intravenous (IV) antibiotics are reserved for patients particularly unwell, unable to take oral treatment or with clinical failure after oral antibiotics[1]. However, a formal grading of bronchiectasis exacerbation severity is not addressed. The Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) uses a classification system based on required medical intervention and patients' clinical signs. Bronchiectasis exacerbations are considered: a) mild or moderate when controlled with oral antibiotics; b) severe when IV antibiotics or hospitalisation is required or if at least one

of the following conditions is present: exacerbated acute or chronic respiratory failure, significant deterioration in oxygen saturation, high temperature or other criteria for sepsis, frank haemoptysis or significant deterioration in lung function; and c) very severe in the presence of haemodynamic instability, altered level of consciousness or need for admission to an intensive or intermediate care unit[23]. The concept of "mild" exacerbations with symptoms that are worse than the day-to-day variation, but do not result in antibiotic treatment has not been universally accepted to date. In the future, the development and validation of severity scores for grading bronchiectasis exacerbations may help clinicians predict patients' prognosis, and consequently make more evidence-based decisions about their management.

In the last years, two multidimensional scoring systems, the Bronchiectasis Severity Index (BSI)[12] and the FACED (F - forced expiratory volume in first second, A - age, C - chronic infection with *Pseudomonas aeruginosa*, E - radiological extension, D - dyspnoea) score[24] have been developed to predict bronchiectasis prognosis, as will be discussed below. These scores were originally created and validated in stable patients and are not designed to determine the severity of exacerbations.

EPIDEMIOLOGY

Over recent years, there has been a paradigm shift towards increased awareness of bronchiectasis among clinical and research community. Historically described as an "orphan disease", it has become one of the most recognised chronic respiratory diseases, following chronic obstructive pulmonary disease (COPD) and asthma[1,25]. However, given the paucity of research data, its real incidence and prevalence remain unclear.

There is growing evidence that incidence and prevalence of bronchiectasis and associated hospitalisations are increasing. The highest bronchiectasis prevalence rates have been reported in the United Kingdom (2013: 566.1 per 100,000 inhabitants in men and 485.5 per 100,000 inhabitants in women) and Catalonia (2012: 362 per 100,000 inhabitants)[20,26]. In 2013, Ringshausen et al.[27] based on International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10) diagnosis codes found a much lower prevalence in Germany of 67 per 100,000 inhabitants. As described by the authors, this methodology could underestimate the true prevalence of bronchiectasis. In a previous study, they showed an increase in the number of hospitalisations for bronchiectasis as the primary diagnosis per year between 2005 and 2011 (from 1449 to 2009)[8]. Seitz et al.[9] demonstrated a similar trend in the US, with an average annual increase of hospitalisations for bronchiectasis of 2.4% and 3.0% for men and women, respectively between 1993 and 2006.

A prospective cohort study with a 4-year follow-up by Chalmers et al.[12] enrolling 608 bronchiectasis patients found that: 1) 31.1% of patients were admitted to the hospital or emergency department; 2) 13.3% of patients had > 1 hospitalisation; and 3) the mean exacerbation frequency was 1.8 per year. Recent European data showed that 40 to 60% of European bronchiectasis patients had ≥ 2 exacerbations per year and one third required at least 1 hospitalisation per year[12]. These numbers are a matter of concern due to the significant impact of

exacerbations on the overall prognosis of bronchiectasis patients.

A prospective study by Loebinger et al.[28] including 91 bronchiectasis patients followed from 1994 to 2007 found a death rate of 29.7%, which was higher than expected according to life expectancy data from the same population (expected death rate was 14.7% and 8.9% for men and women, respectively). Bronchiectasis, respiratory infection or respiratory failure were considered the cause of death in more than 70% of cases. A more recent study by Quint et al.[20] reported that mortality for patients with bronchiectasis was more than twice the mortality for the general population, independent of sex (women: 1437.7 versus 635.9 per 100,000 inhabitants; men: 1914.6 versus 895.2 per 100,000 inhabitants).

Overall, there is little evidence on bronchiectasis exacerbations impact on patients' daily symptoms, QoL or lung function. Brill et al.[6] showed that during an exacerbation, symptoms last for more than two weeks; after 35 days, 16% of patients had not returned to their pre-exacerbation state. They also found an increase of 6.3 units in COPD Assessment Test (CAT) and a reduction of 10.6% or 31L/min in peak expiratory flow rate (PEFR) during an exacerbation. A previous small study, suggested that more frequent severe exacerbations (≥ 1.5 per year) were associated with accelerated decline of lung function[29]. However, further large prospective studies are needed to clarify these results and assess patients' outcomes during and after exacerbations of bronchiectasis.

The economic burden of bronchiectasis is considerable. The annual cost of bronchiectasis treatment was estimated by De La Rosa et al.[10] at 4671.9 euros per patient. This study also showed that the number of hospitalisations was independently associated with higher costs. Bibby et al.[11] reported an annual cost for hospitalisations of 5.34 million New Zealand Dollar (NZD).

In summary, this research evidence and clinical experience are the rationale to consider exacerbations as one of the most important outcome measures in bronchiectasis.

AETIOLOGY OF EXACERBATIONS

The aetiology of bronchiectasis exacerbations is not fully understood, but there have been described distinct causes and triggers such as bacterial and viral infections and air pollution.

The most common isolated bacteria in the sputum cultures of patients with bronchiectasis exacerbations are *Pseudomonas aeruginosa*, *Haemophilus influenzae*, *Enterobactericeae*, *Streptococcus pneumoniae*, *Staphylococcus aureus* and *Moraxella catarrhalis*. However, it has been increasingly recognised, through clinical experience and limited evidence data that the same microorganisms are also isolated when the patient is clinically stable[30-32]. The challenge is clarifying why these patients exacerbate. Three possible explanations have been suggested: 1) emergence of a new bacteria strain; 2) increase of bacterial load of existing bacteria; and 3) changes in bacterial virulence[33]. Microbiome studies, based on 16S ribosomal RNA gene sequencing have revealed that the diversity of bronchiectasis microbiota is considerably higher than anticipated, including potentially pathogenic and non-pathogenic aerobic and anaerobic species. In the small number of microbiota studies performed to

date that compared patients at exacerbation and when stable, no significant differences or consistent patterns have been found to account for exacerbations[34-37].

Atypical bacteria and viruses play a major role in exacerbations of chronic respiratory diseases, such as COPD and asthma[38,39]; however, this is not yet demonstrated in bronchiectasis. Metaxas et al.[40] described that in a cohort of 15 patients with a total of 19 exacerbations over 2 years, polymerase chain reaction (PCR) and serology for detection of *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and respiratory syncytial virus (RSV) in bronchoalveolar lavage samples were all negative. A prospective 1-year study by Gao et al.[41] enrolling 58 patients with a total of 100 exacerbations detected viruses in nasopharyngeal swabs and sputum samples by PCR more frequently during bronchiectasis exacerbations rather than during steady state (49% versus 18.9%), suggesting that they can be an exacerbation trigger in a significant number of patients. Furthermore, virus-positive patients were more likely to be treated with IV antibiotics.

Allergic bronchopulmonary aspergillosis (ABPA), associated with hypersensitivity to *Aspergillus fumigatus* is a cause of bronchiectasis in 4-8% of patients, and it should always be considered at diagnosis[2,42,43]. However, overall, the pathogenic significance of fungi in bronchiectasis "vicious cycle" is not yet elucidated. The most frequent species cultured in clinically stable patients are *Candida albicans* and *A. fumigatus*, and they are mostly isolated with bacteria and in patients receiving chronic antibiotics[44,45]. Whether fungi are relevant to exacerbations or just "co-cultured microorganisms" of pathogenic bacteria has not been examined. Further studies are needed to clarify the potential causal relationship between atypical bacteria, viruses or fungi infection and bronchiectasis exacerbations.

Exposure to indoor and outdoor air pollutants are well described triggers of exacerbations of COPD, asthma and idiopathic pulmonary fibrosis (IPF). In bronchiectasis, Goeminne et al.[46,47] suggested that air pollution is associated with a higher risk of exacerbations or death. However, the specific effect of different air pollutants in this disease needs to be elucidated.

RISK FACTORS OF EXACERBATIONS

Recently there has been a lot of research on risk factors for bronchiectasis exacerbations. A large cohort study, including 2596 patients from Europe and Israel showed that overwhelmingly the strongest predictor of future events was a past history of frequent exacerbation. In addition, chronic infection with *P. aeruginosa* and *H. influenzae*, worse lung function, radiological severity and co-existing COPD were associated with increased exacerbation risk[48]. The authors also first described a "frequent exacerbator phenotype" in bronchiectasis that was stable over time (3 years follow-up) and associated with worse QoL, more frequent hospitalisations and increased mortality over up to 5 years[48]. Another recent study with the same cohort of patients showed that mortality was increased in those with two or more exacerbations per year, especially in the presence of *P. aeruginosa* chronic infection (hazard ratio [HR] 2.03; 95% confidence interval [CI] 1.36-3.03)[49].

Bronchiectasis Severity Index (BSI)[12] is a well-validated predictive tool that objectively

stratifies patients into mild, moderate and severe risk groups for mortality, hospitalisations, future risk of exacerbations and QoL. The predicted risk of hospitalisation at four years varies between 0-9.2% to 41.2-80.4% for mild and severe patients, respectively. The data used to derive BSI showed that body mass index (BMI), FEV_1% predicted, previous exacerbations (with and without hospitalisation), Medical Research Council (MRC) dyspnoea score and chronic infection, especially with *P. aeruginosa* and *methicillin-resistant Staphylococcus aureus* were risk factors for future exacerbations. Undoubtedly, the strongest independent predictors of hospitalisation and mortality were previous hospitalisation and age, respectively.

The FACED score[24] incorporating FEV_1% predicted, age, *P. aeruginosa* chronic infection, radiological extent of the disease, and dyspnoea was originally developed to predict mortality in bronchiectasis patients. Last year, a modified version including the variable "at least one severe exacerbation in the previous year" was created (E-FACED score) to improve predictive capacity of exacerbations[50].

A meta-analysis by Finch et al.[51] demonstrated that *P. aeruginosa* chronic infection was an independent risk factor for hospitalisation and death: these patients had approximately one more exacerbation per year compared to patients without *P. aeruginosa* chronic infection. In addition, Aliberti et al.[2] documented that patients with chronic infection (with *P. aeruginosa* or other microorganisms) had a higher number of exacerbations during 1-year follow-up than patients without chronic infection.

Therefore, bacterial infection is a consistent risk factor for future exacerbations. Not only the presence of bacteria, but also the load appears to be important. A higher bacterial load in patients with clinically stable bronchiectasis has been identified as a significant predictor of recurrent (≥ 3) exacerbations and hospitalisation[52].

Several co-morbidities have been associated with exacerbation risk in chronic respiratory diseases. COPD, asthma, rhinosinusitis, gastro-esophageal reflux and severe vitamin D deficiency were all described as risk factors of exacerbations in bronchiectasis patients[25,53-58].

Our knowledge of molecular biology and genetics of bronchiectasis exacerbations is very limited. Recently, Chalmers et al.[59] showed that elevated sputum neutrophil elastase activity was associated with a higher risk of exacerbations (independently of severity) and a higher lung function decline. We also demonstrated that at the onset of an exacerbation sputum elastase activity increased and after antibiotics returned to baseline levels. Mannose-binding lectin (MBL) deficiency has also been associated with increased bronchiectasis exacerbations and hospitalisations[60].

In addition to these important risk factors of typical bronchiectasis exacerbations, clinicians should take into account that patients may suffer exacerbations of underlying diseases such as COPD, asthma, ABPA or other co-morbidities[61]. It is important therefore to consider co-morbidities and underlying conditions in evaluating patients with frequent bronchiectasis exacerbations.

Ultimately it should be noted that some of these risk factors, namely *P. aeruginosa* infection, higher bacterial load and co-morbidities could be considered "modifiable", and consequently

should be focus of our attention in daily clinical practice, as will be discussed below.

PREVENTION OF EXACERBATIONS

Prevention of exacerbations, a key goal in bronchiectasis management, mainly concerns the optimisation of multifaceted pharmacological and non-pharmacological interventions. However, specific data on the benefits of these interventions used in daily practice are limited and contradictory. Figure 2 presents a list of interventions that are used to prevent exacerbations. Table 1 shows the 2017 guidelines for the management of adult bronchiectasis by the European Respiratory Society (ERS) focusing on prevention of exacerbations[19].

General management

Although not extensively explored, there are a number of plausible strategies that could influence bronchiectasis patients' prognosis, namely reduce the frequency and/or the severity of exacerbations such as education, smoking cessation, influenza and pneumococcal vaccination, treatment of the underlying causes of bronchiectasis (e.g., common variable immunodeficiency and ABPA), management of co-morbidities and adequate nutrition[1,12,19,23,25,58,62,63]. From a clinical perspective, patient-centred education and shared-management programmes are particularly important; they have been widely reported as essential components of personalised care planning in chronic respiratory diseases. Their therapeutic value in bronchiectasis has not been clearly documented, but some limited data and daily clinical experience shows that they represent a key element to improve symptoms self-management, QoL and therapeutic compliance[1,23,33,64-67].

Airway clearance techniques and pulmonary rehabilitation

The 2017 ERS bronchiectasis guidelines strongly advocate airway clearance techniques (ACTs). Recently, the largest randomized control trial (RCT) in this field, that included 44 patients randomised to perform twice daily ELTGOL (slow expiration with the glottis opened in the lateral posture) technique (n = 22) or placebo exercises (n = 22) over 1 year, showed that patients in the ELTGOL group had significantly reduced bronchiectasis exacerbations and improved QoL[68]. A previous Cochrane review concluded that ACTs appear to be safe and may account for improvements in sputum expectoration, symptoms, lung function and QoL[69]. A small 3-month randomised crossover trial comparing twice daily chest physiotherapy using an airway oscillatory device with no chest physiotherapy did not find a significant difference in the number of bronchiectasis exacerbations (secondary outcome)[70].

Although mucus clearance could be considered the cornerstone of prevention of bronchiectasis exacerbations, no form of ACT has been shown to be superior to another. A variety of manual and instrumental techniques are available, and they should be tailored to each patient's needs, goals and preferences, being part of an appropriate personalised treatment[1,19,23,25,33,69,71].

It is important to emphasise that, when one is considering a "step-up" treatment, namely long-term antibiotic, it is always essential to

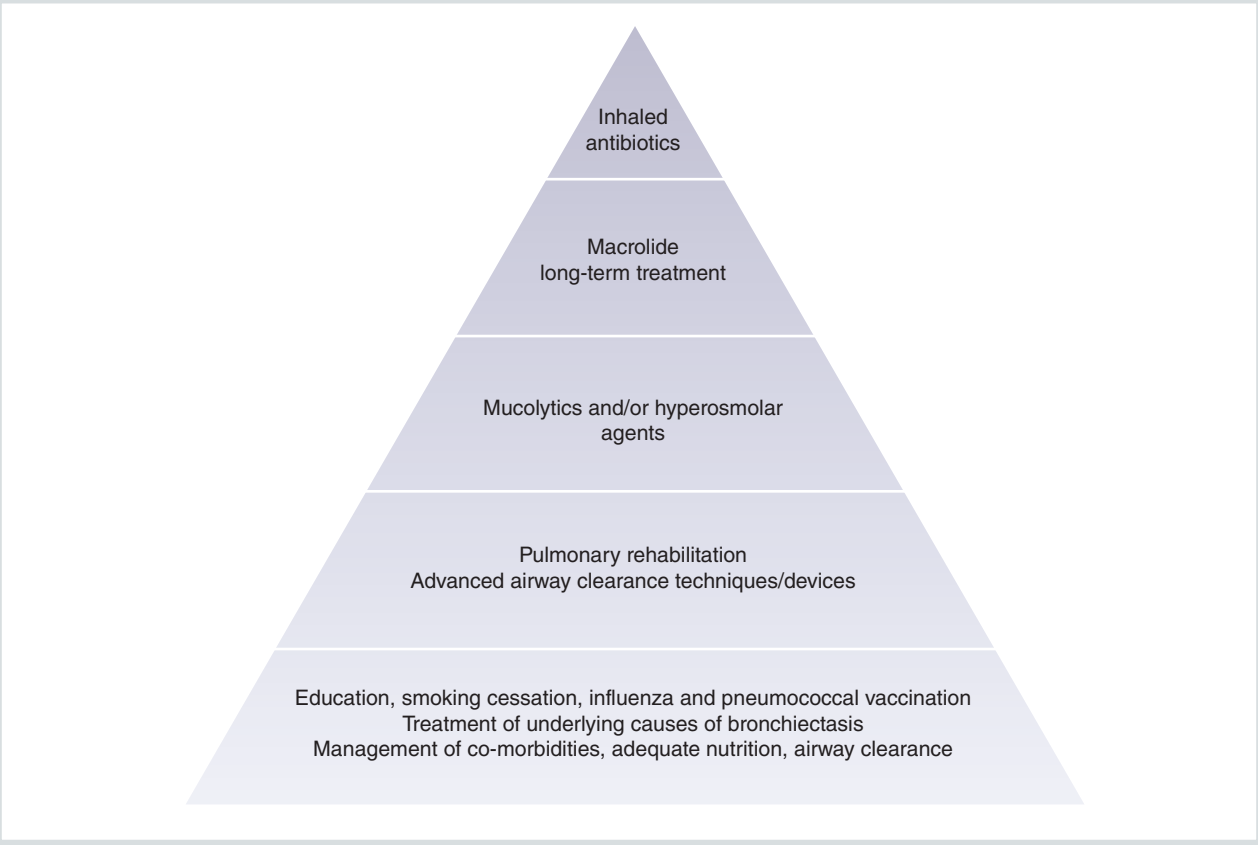

Figure 2. Key management components in the prevention of bronchiectasis exacerbations. The base of the pyramid shows interventions that should be considered for all patients, with interventions becoming more selective as the pyramid goes higher.

Table 1. Summary of ERS recommendations focusing on prevention of adult bronchiectasias exacerbations

Eradication treatment	– Offering eradication antibiotic treatment following new isolation of *P. aeruginosa* – Not offering eradication antibiotic treatment following new isolation of pathogens other than *P. aeruginosa*
Long-term antibiotic treatment	– Offering long-term antibiotic treatment for patients with ≥ 3 exacerbations per year – Offering long-term inhaled antibiotic treatment for patients with chronic *P. aeruginosa* infection AND ≥ 3 exacerbations per year – Offering long-term macrolides (azithromycin or erythromycin) for patients without chronic *P. aeruginosa* infection AND ≥ 3 exacerbations per year – Considering long-term antibiotic treatment only after optimisation of general aspects of bronchiectasis management
Long-term mucoactive treatment	– Offering long-term mucoactive treatment in patients who have difficulty in expectorating sputum and poor quality of life where standard airway clearance techniques have failed to control symptoms – Not offering recombinant human DNase
Regular physiotherapy	– Patients with chronic productive cough or difficulty to expectorate sputum should be taught an airway clearance technique by a trained respiratory physiotherapist to perform once or twice a day – Patients with impaired exercise capacity should participate in a pulmonary rehabilitation programme and take regular exercise

ERS guidelines provide other recommendations for the management of adult patients with bronchiectasis not addressed in this table *(reproduced and modified with permission from Polverino E et al.[19]).*
DNAse: deoxyribonuclease; ERS: European Respiratory Society.

review adherence to airway clearance and other prescribed therapies. In the authors' opinion, all clinicians involved in bronchiectasis care should keep in mind what was referred by Baum[72] in 1996: "the story of patients receiving course after course of antibiotics for the symptoms of bronchiectasis without use of physical measures is a recurrent one, in my experience".

Unlike in COPD where pulmonary rehabilitation has a well described benefit in symptoms, health status and exercise capacity, little has been studied about its impact on bronchiectasis patients. Lee et al.[69] showed that 8 weeks of supervised exercise training and review of ACTs reduced the number of exacerbations over 12 months, prolonged the time to first exacerbation (6 versus 8 months) and was associated with short-term improvement in dyspnoea, fatigue and exercise capacity. A pulmonary rehabilitation programme usually also poses a unique opportunity to educate, review of potential co-morbidities such as cardiovascular disease and osteoporosis, screen for malnutrition, address psychosocial issues such as anxiety and depression, and promote regular physical activity, all essential components of management of bronchiectasis patients.

Mucolytic and hyperosmolar agents

It is not clear whether nebulised hypertonic saline 3-7% prevents bronchiectasis exacerbations. Nicolson et al.[73] showed that daily treatment with hypertonic saline 6% or isotonic saline 0.9% for 12 months had similar effects on exacerbation frequency. In contrast, Kellet et al.[74] demonstrated a significant decrease in the antibiotics and emergency healthcare use in patients treated with hypertonic saline 7% for 3 months, when compared to isotonic saline 0.9%.

Treatment with inhaled mannitol or nebulised deoxyribonuclease (DNase) is not advisable in bronchiectasis. Bilton et al.[75] showed that inhaled mannitol 400mg (versus mannitol 50mg) twice a day for 52 weeks did not significantly reduce exacerbations rates (primary endpoint) but prolonged the time to first exacerbation and improved QoL (secondary endpoints). In 1998, O'Donnell et al.[76] suggested that nebulised DNase was ineffective, and even potentially harmful in idiopathic bronchiectasis patients. Since then, no more studies with this drug were performed.

Oral N-acetylcysteine or carbocisteine with known mucolytic and antioxidant proprieties are widely used in bronchiectasis patients, but their benefit has not yet been explored in clinical trials[77].

Long-term antibiotic treatment – inhaled or oral

While inhaled antibiotics have strong placebo-controlled trial evidence of exacerbations reduction in CF, particularly those chronically infected with *P. aeruginosa*, there remains controversy about their role in bronchiectasis. Clinical experience and some RCTs have shown beneficial effects of inhaled gentamicin, colistin and ciprofloxacin on exacerbation frequency and/or time to first exacerbation specifically in bronchiectasis patients[13,14,16-18]. However, two large trials reported that aztreonam did not prolong the time to first exacerbation (secondary outcome)[15]. The Ciprofloxacin Dry Powder

for Inhalation in Non-cystic Fibrosis Bronchiectasis (RESPIRE) trials, the largest clinical trial programme to date in bronchiectasis, have recently been reported. These trials tested ciprofloxacin dry powder for inhalation (DPI) versus placebo in 2 x 14-day on/off arms and 2 x 28-day on/off arms in a multicentre RCT. The trials gave inconsistent results with significant reductions in frequency of exacerbations and prolonged time to first exacerbation in the 14-day on/off arm in RESPIRE 1, but no statistically significant benefit in the other arms. Pooled data suggested a clear benefit of treatment[17-18]. Detailed description of these studies is shown in Table 2.

Three RCTs, Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE), Bronchiectasis and Long-term Azithromycin Treatment (BAT) and the Bronchiectasis and Low-dose Erythromycin Study (BLESS) involving a total of 341 patients showed that long-term oral azithromycin (500mg three times a week or 250mg once a day) or erythromycin (400mg twice a day) are effective in reducing the number of exacerbations[78-80].

The summary of ERS guidelines recommendations for long-term antibiotic treatment are shown in figure 3[19]. The ideal length of inhaled or oral antibiotic treatment is uncertain. ERS guidelines define "long-term treatment" as at least 3 months[19] and the published data are from 6- or 12-month RCTs[78-80]. Thus, in clinical practice it is common to treat patients for at least 6 to 12 months to confirm or exclude clinical benefit, unless adverse events lead to treatment discontinuation.

A major concern about long-term antibiotic (inhaled and oral) treatment is microbial resistance[19]. A prospective observational study by Menéndez et al.[32] identified three independent risk factors associated with isolation of multidrug-resistant (MDR) pathogens in bronchiectasis exacerbations: chronic renal disease, prior MDR isolation and hospitalisation in the previous year. Notably, MDR isolation was more frequent in patients using inhaled antibiotics (34.4% versus 19.7%), but there was no statistically significant difference. To understand the possible impact of long-term antibiotics on the emergence of microbial resistance is a research priority in bronchiectasis[33].

TREATMENT OF EXACERBATIONS

Since bacterial infection has been recognised as the most frequent cause of bronchiectasis exacerbations, its treatment has been focused on antibiotics and other adjuvant therapies. However, there is a limited body of good-quality evidence regarding: 1) choice of antibiotic and dosage regimen; 2) monotherapy versus combination treatment; and 3) length of treatment[19].

From a clinical perspective, physicians assume a different therapeutic approach driven by exacerbation severity, previous positive sputum cultures, presence of *P. aeruginosa* infection and co-morbidities[1,23].

Before starting antibiotics, it is recommended to review patient's previous sputum microbiology and antimicrobial susceptibility to guide antibiotic choice, and to send at least a sputum sample for culture[1,19].

Table 2. Summary of RCTs investigating the effect of inhaled antibiotics on exacerbation frequency and/or time to first exacerbation

Study and first author	Antibiotic	Scheme of administration	Number of patients (completed the study)	Exacerbation frequency	Time to first exacerbation (days)
Murray et al.[13]	Gentamicin	Nebulised gentamicin (80 mg) or placebo (0.9% saline) twice a day for 12 months	57	✓ 0 (0–1) versus 1.5 (1–2); p < 0.0001	✓ 120 (87–161.5) versus 61.5 (20.7–122.7); p = 0.02
Haworth et al.[14]	Colistin	Colistin (1 million IU) or placebo (0.45% saline) via the I-neb twice a day for up to 6 months	144	Not evaluated	× 165 (42) versus 111 (52); p = 0.11 ✓ 168 (65) versus 103 (37); p = 0.038 in adherent patients (taking > 80% of doses)[#]
AIR-BX1 AIR-BX2 Barker et al.[14]	Aztreonam	Nebulised aztreonam (75 mg) or placebo three times a day, in 2 treatment cycles of 28 days on/off	AIR-BX1: 266 AIR-BX2: 274	× AIR-BX1: 1.32 versus 1.08; p = 0.35 AIR-BX2: 1.20 versus 1.14; p = 0.81	Median time to first exacerbation was only reached in one group as study was only 2 cycles (placebo in AIRBX1)
ORBIT II Serisier et al.[16]	Ciprofloxacin	Nebulised dual release ciprofloxacin (liposomal ciprofloxacin 150 mg in 3 ml and free ciprofloxacin 60 mg in 3 ml) or placebo once a day, in 3 treatment cycles of 28 days on/off	42	Not evaluated	134 versus 58; p = 0.057 mITT, p = 0.046 per protocol
RESPIRE 1 De Soyza et al.[17]	Ciprofloxacin	Ciprofloxacin DPI 32.5 mg or placebo in 2 treatment regimens consisting of on/off treatment cycles of 14 or 28 days for 48 weeks	334	✓ Ciprofloxacin DPI 14 days on/off: 0.6 versus 1.0; p = 0.0061* × Ciprofloxacin DPI 28 days on/off: 0.8 versus 0.8; p = 0.8946	✓ Ciprofloxacin DPI 14 days on/off: > 336 versus 186; p = 0.0005* × Ciprofloxacin DPI 28 days on/off: 336 versus 186; p = 0.0650
RESPIRE 2 Aksamit et al.[18]	Ciprofloxacin	Ciprofloxacin DPI 32.5 mg or placebo in 2 treatment regimens consisting of on/off treatment cycles of 14 or 28 days for 48 weeks	442	× Ciprofloxacin DPI 14 days on/off: IRR 0.83; p 0.2862* Ciprofloxacin DPI 28 days on/off: IRR 0.55; p 0.0014*	× Ciprofloxacin DPI 14 days on/off: HR 0.87; p 0.3965* Ciprofloxacin DPI 28 days on/off: HR 0.71; p 0.0511*

Data presented as median and interquartile range (IQR) or mean and standard deviation (SD) as appropriate.
✓ Met outcome(s).
× Unmet outcome(s).
[#]Primary outcome.
*Predefined statistical significance level: p=0.049 for the 14-day regimen and p=0.001 for the 28-day regimen.
DPI: dry powder for inhalation; HR: hazard ratio; IRR: incidence rate ratio; IU: international unit; mITT: modified intention to treat; RCT: randomised clinical trial.

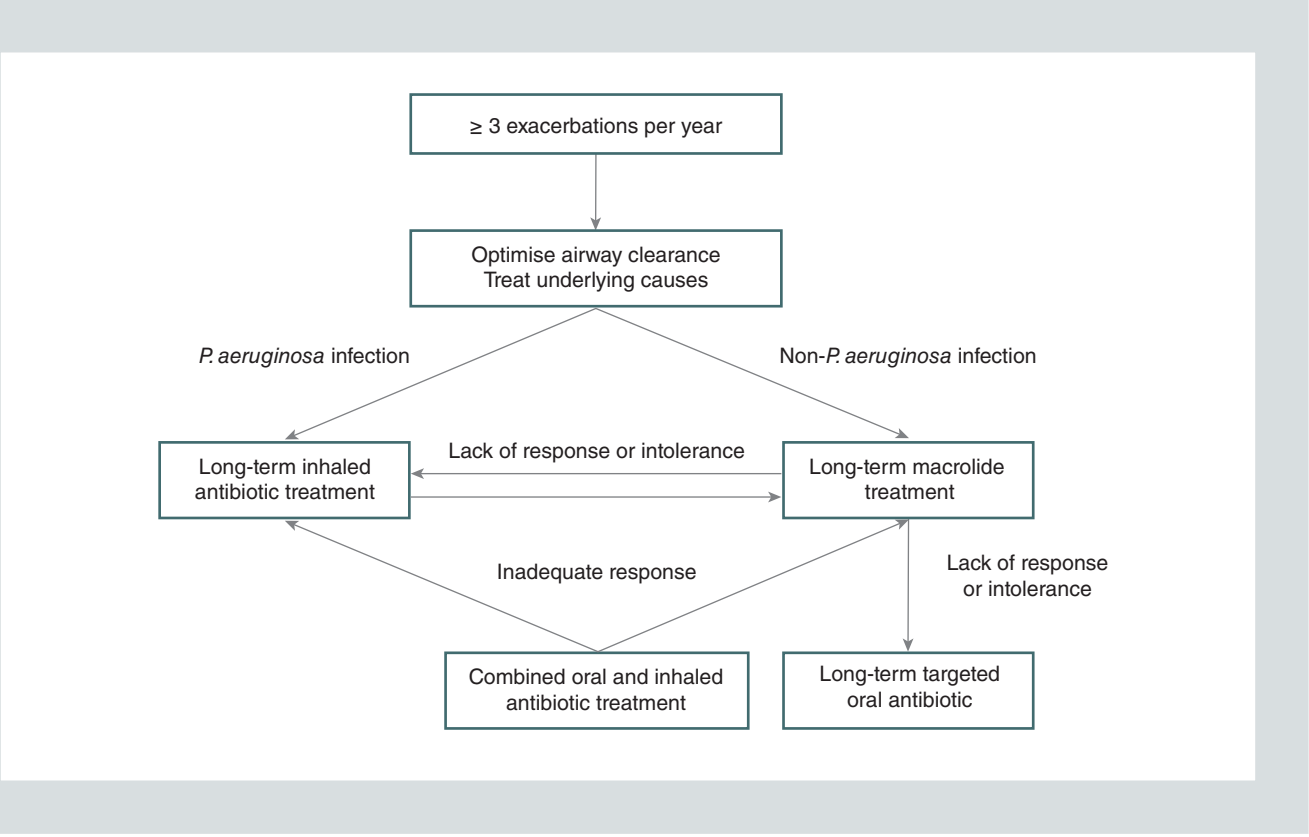

Figure 3. Summary of recommendations for long-term antibiotic treatment *(reproduced with permission from Polverino E et al.[19]).*

The majority of bronchiectasis exacerbations are treated with oral antibiotics. Intravenous treatment is reserved for severe exacerbations, namely requiring hospitalisation or after failure of oral treatment[1].

Many physicians recommend combination treatment, ideally with two antibiotics with different mechanisms of action and resistance development (e.g., beta-lactam or antipseudomonal cephalosporin plus aminoglycoside) if there is evidence of *in vitro* resistant *P. aeruginosa* infection or if the patient is likely to require many subsequent courses of antibiotics1. This is common practice in CF. It must be noted that the bronchiectasis population is significantly older and more co-morbid than CF patients, and so the risks of drugs such as aminoglycosides used systematically may be higher.

It is a common belief that bronchiectasis exacerbations require a more prolonged antibiotic course at higher doses than other acute respiratory infections, namely pneumonia. Current guidelines suggest that bronchiectasis exacerbations should be treated with 14 days of antibiotics. However, the ERS task force panel recognised the possibility to treat some selected cases with shorter courses of antibiotics, namely mild exacerbations, exacerbations in mild patients, those associated with pathogens more sensitive to antibiotics (e.g. *Streptococcus pneumoniae*), or patients with a rapid return to baseline state[1,19,23].

To date no studies have evaluated the clinical relevance of short- or long-acting bronchodilators, inhaled or systemic corticosteroids, mucoactive drugs or ACTs in bronchiectasis exacerbations. However, there is some evidence that patients with bronchiectasis exacerbations may benefit from intensification of bronchodilator treatment or even a course of oral corticosteroids if they have asthma or COPD. Furthermore, BTS guidelines suggested that patients should maintain ACTs during an exacerbation and the addition of manual techniques should be considered[1]. Therefore, alongside antibiotic treatment, physicians should address whether the patient requires additional help with airway clearance, bronchodilator treatment, systemic corticosteroids (in the case of co-existing airways disease), intravenous fluid treatment and other supportive measures.

FUTURE CHALLENGES

There remain many unanswered questions regarding our understanding of bronchiectasis exacerbations. It is likely that just as bronchiectasis is heterogeneous, exacerbations are likely to be equally heterogeneous. A deeper understanding of the mechanisms leading to exacerbations and a recognition of phenotypes and endotypes of exacerbations may lead to more targeted treatment and successful clinical trials. Understanding the role of bacteria, viruses, fungi and non-infectious stimuli in triggering exacerbations are now vital to designing more effective preventative measures. Further clinical trials are needed to establish the efficacy of measures to reduce exacerbations, including mucoactive drugs and antibiotic approaches. The research priorities in bronchiectasis have been well described recently by the EMBARC network, including a large number of proposed studies around the topic of exacerbations[33,81].

CONCLUSIONS

Prevention of exacerbations, a serious and frequent complication of bronchiectasis is a priority goal in daily clinical practice. Recently developed prognostic scores aid clinicians to identify patients at risk of future events, guiding individually tailored strategies. However, further research is needed to analyse the effectiveness of current approaches and to explore new strategies that could support evidence-based decision making. The recent consensus definition of bronchiectasis exacerbations should help to standardise outcomes in upcoming clinical trials.

CONFLICTS OF INTEREST

Dr. Chalmers reports grants and personal fees from Glaxosmithkline, grants and personal fees from Boehringer-Ingelheim, grants from Astrazeneca, grants and personal fees from Pfizer, grants and personal fees from Bayer Healthcare, grants and personal fees from Grifols, personal fees from Napp, outside the submitted work.

The rest of the authors have no conflict of interest to declare.

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