Review Article

Exacerbations of bronchiectasis in adults

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ABSTRACT

Exacerbations are significant events in the course of bronchiectasis. Exacerbations are associated with accelerated lung function decline and deterioration in quality of life (QoL). Prevention of exacerbations is therefore one of the key objectives of management of bronchiectasis. A few treatments have been proven to reduce the risk of exacerbations, but these include the treatment of underlying causes of bronchiectasis and the use of prophylactic antibiotic therapies (macrolides and inhaled antibiotics). Nonantibiotic therapies, such as airway clearance and pulmonary rehabilitation, also play an important role in the prevention of exacerbations. Acute exacerbations are treated with antibiotics directed against the known bronchiectasis pathogens and guided by previous sputum culture results. This emphasizes the importance of screening sputum cultures in stable patients. Assessment of severity is used to determine whether patients should be treated at home or in hospital. Supportive therapy for exacerbations should include airway clearance alongside oxygen, hydration, and treatment of bronchospasm as required. Bronchiectasis is a rapidly developing field and new therapies, both for the prevention of exacerbations and the treatment of acute exacerbations, are currently being developed.

Key words: Antibiotics, bronchiectasis, exacerbation, infection, microbiology, prognosis

INTRODUCTION

Bronchiectasis is a common chronic respiratory disease presenting with cough, sputum production, respiratory infections, and impaired QoL.[1,2] The cause is unknown in a majority of cases and the management remains largely empirical due to the absence of large-scale clinical trials.[1,2]

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The exact prevalence is not known, but recent estimates of prevalence are 67/100,000 in Germany and 485/100,000 in men and 566/100,000 in women in the UK.[3,4] Extrapolating this to the European Union as a whole, we might expect at least 350,000 patients with bronchiectasis in the EU, increasing to 2,500,000 patients if the data from the UK are generalizable across Europe.[3] This compares to approximately 70,000 patients with cystic fibrosis (CF) worldwide and an incidence of chronic obstructive pulmonary disease (COPD) of approximately 7% in Europe.[5-7] Consequently, it might be estimated

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that there are 15–100 cases of COPD for every case of bronchiectasis.

Although bronchiectasis has historically been a neglected disease, a resurgence in interest in the disease over the past several years has generated a volume of new evidence that improves our understanding of the disease.[8] Exacerbations of bronchiectasis account for a large proportion of the clinical workload and the economic impact of bronchiectasis on health care systems internationally.[8-10] This article aims to review the epidemiology and clinical aspects of bronchiectasis exacerbations, with a focus on optimal management and prevention.

DEFINITION AND EPIDEMIOLOGY OF EXACERBATIONS

The precise definition of an exacerbation is important from a clinical research standpoint where it is used as the primary outcome in clinical trials but is of lesser importance in clinical practice where patients can usually recognize and report their typical symptoms of exacerbation and where operationally, it is most useful to think of exacerbations as deteriorations in the patient's respiratory symptoms that are persistent and greater than the usual day-to-day variation of the condition and that patient and clinician agree requires treatment.

We have previously reviewed more than 10 definitions of exacerbations used in the literature.[11]

Some definitions include minor and major symptoms, for example, at least three major criteria of increasing sputum production, change in sputum color, increased dyspnea or increased cough, or two of the above major criteria and at least two minor criteria such as fever, malaise/fatigue, fall of 10% in lung function, or new hemoptysis.[12] Fuchs criteria, used in CF, have also been used in bronchiectasis consisting of a deterioration in at least 4 of 9 criteria (sputum production, dyspnea, cough, fever, wheezing, exercise tolerance, forced expiratory volume at 1 s [FEV_1] or forced vital capacity, new changes in chest radiograph, or changes in chest auscultation).[13,14]

The British Thoracic Society (BTS) defines exacerbation as the deterioration of at least three respiratory symptoms (cough, increased sputum production, volume, purulence or change in viscosity with or without increasing wheeze, increased dyspnea, hemoptysis, and chest pain) for >24 h and/or systemic complaints, such as fever, and alterations in chest radiograph.[2]

Spanish Society of Pneumology and Thoracic Surgery defines exacerbation as an increase of volume and purulence in sputum or a change in sputum consistence/viscosity (or hemoptysis) with or without systemic complaints such as fever, cough, asthenia, anorexia, weight loss, and pleural pain.[15]

Large cohort studies suggest that patients with bronchiectasis experience an average of 1–2 exacerbations per year.[16-20] Within such estimates, there are approximately one-fourth of patients who may not have experienced any exacerbation in the previous year and 40–60% of patients who experience two or more exacerbations per year.[16] Whether there is a consistent "frequent exacerbator" phenotype in bronchiectasis, as has been described in COPD, is not clear.[21]

Exacerbations in bronchiectasis have traditionally been viewed as being exclusively bacterial. We now recognize from epidemiological data that although bacterial infection is common, raised airway bacterial load, neutrophilic inflammation, and presence of specific bacteria such as *Pseudomonas aeruginosa* are risk factors for exacerbations, so are a number of nonbacterial causes.[22-25] These include respiratory viruses, air pollution, and comorbidities which have all been shown to increase the risk of exacerbations or to be present at exacerbation.[26-30] Exacerbations are therefore likely to be heterogeneous events driven by infectious and noninfectious stimuli as have been observed in other diseases such as COPD.[27] Nevertheless, the relationship is complex, as at least in COPD, viral infections appear to suppress local antibacterial immunity precipitating an increase in airway bacterial load.[31]

MICROBIOLOGY OF EXACERBATIONS

Clinical experience, and what limited data have been published on the microbiology of exacerbations, suggests that patients will most frequently isolate the same bacterial species that they typically grow in sputum when stable.[32] Thus, patients colonized with *P. aeruginosa* will typically grow this organism at exacerbation and similarly for *Haemophilus influenzae* or other common organisms.[22] Studies have not been conducted to know whether exacerbations are associated with an increase in bacterial load of a preexisting bacterial strain or whether exacerbation is associated with acquisition of new strains as has been observed in COPD.[33] Patients may also isolate new pathogens at exacerbation, including first isolation of *P. aeruginosa* which emphasizes the importance of sending sputum for culture at the onset of an exacerbation and also for treating with antibiotics that cover the most likely causative organisms, as will be discussed below.

Although fungi and viral infections are a cause of exacerbations in patients with chronic airway diseases, their roles in bronchiectasis remain unclear. Some studies show that prevalence of viral infections, detected by polymerase chain reaction (PCR) assay in nasopharyngeal swabs and sputum samples, is higher during bronchiectasis exacerbations than in steady state, suggesting that respiratory viruses can play a crucial role in triggering exacerbations.[29] In a study of 100

exacerbations in Southern China, Gao *et al*. found that 49% of patients had a positive nasopharyngeal swab or sputum sample by PCR for viruses at exacerbation, compared to 19% when stable. The most frequent were *Coronavirus*, *Rhinovirus*, and influenza A/B viruses.[29]

PREDICTION OF EXACERBATIONS

We performed a multivariable analysis to identify predictors of severe exacerbation requiring hospital admission.[16] Independent predictors in this cohort of 608 patients were FEV_1 <30% predicted (hazard ratio [HR] 1.52, 95% confidence interval [CI] 1.03-2.25), Medical Research Council dyspnea score, Grade IV (HR 2.42, 95% CI 1.66–3.52) and Grade V (HR 2.69, 95% CI 1.59–4.53), *P. aeruginosa* colonization (HR 2.16, 95% CI 1.36–3.43) and other bacterial colonization (HR 1.66, 95% CI 1.12–2.44), and radiological extent of bronchiectasis (HR 1.48 95% CI 1.02–2.15).[16] This analysis therefore revealed not only that severity of disease in terms of radiological, lung function and symptoms are associated with more severe exacerbations but also that bacterial infection is a key driver. Nevertheless, by far, the strongest predictor in this analysis was a history of previous severe exacerbations (HR 13.5, 95% CI 9.4–19.5). This mirrors data in COPD and other diseases.[16]

The study established a bronchiectasis severity index (BSI), a multidimensional scoring system that predicts future risk of severe exacerbations and mortality in bronchiectasis.[16] The score has an accuracy of 76–88% based on the area under the curve for predicting severe exacerbations requiring hospital admission across 1310 patients in four European countries.[16] Further validation data will be shortly published. For exacerbations not requiring hospital admissions, there is a significant increase in exacerbations in patients with more severe disease according to the BSI. Compared to those with moderate disease, mild patients have 40% fewer exacerbations and severe patients 70% more exacerbations on average.[16]

Predictors of nonsevere exacerbations have been less clearly defined, but individual studies have identified a number of risk factors including underlying etiologies such as asthma, severity of disease, comorbidities such as gastroesophageal reflux disease and rhinosinusitis and biomarkers of neutrophilic inflammation.[22-30]

The role of bacterial colonization appears critical. In a recently published study utilizing cluster analysis to find bronchiectasis phenotypes, four clinical phenotypes in bronchiectasis were identified.[25] The cluster that included the patients with chronic infection with *P. aeruginosa* presented the most severe disease and the highest number of exacerbations and hospitalizations.[25] A systematic analysis of 3683 patients mostly from Europe found that patients colonized with *P. aeruginosa* had approximately one more exacerbation per year compared to patients with other pathogens or none [Table 1].[24]

TREATMENT OF ACUTE EXACERBATIONS

Exacerbations may present in different ways, varying from patients attending in primary care or an outpatient clinic with increased sputum production to those presenting to hospital with severe exacerbations requiring the Intensive Care Unit admission.[41] Nevertheless, the general principals of management are the same.

Antibiotic treatment, optimizing airway clearance, bronchodilators, and supportive therapy are considered the mainstay of treatment in an acute bronchiectasis exacerbation.[2] Nevertheless, there is a lack of studies on the treatment of acute exacerbation and so much is extrapolated from CF or COPD.

Early treatment of exacerbations is recommended to limit the vicious circle of infection/inflammation that is a determining factor of lung damage.[23]

Assessment and severity

Managing patients with exacerbations requires an assessment of severity of the exacerbation and decision about whether to treat the patient in the community or in hospital.[2]

Exacerbation is considered severe if the patient develops respiratory failure, hypercapnia, tachypnea (>25/min), hemodynamic instability, or cognitive deterioration.[2] Others authors include fever (>38°C) and hemoptysis. If the exacerbation is severe or if patient is unable to take oral therapy, intravenous (IV) antibiotic therapy should then be considered.[2] The same recommendation applies if patient has a clinical failure after appropriate oral antibiotics. Before determining that oral antibiotics have been ineffective, it is important to obtain a sputum culture and ensure that the oral antibiotic is active against the causative pathogen.[2] Domiciliary IV therapy is highly efficient in terms of saving the costs of hospital treatment and is also usually preferred by patients.[42]

Regarding the facilities for domiciliary IV therapy, there are different realities across European countries.[43] In hospitals with no facilities for domiciliary IV therapy, inpatient treatment should be performed if IV therapy is needed.

The BTS recommends also treatment in an inpatient context if the patient is unable to cope at home, if develops cyanosis, confusion, breathlessness with respiratory rate ≥25/min, temperature ≥38.8°C, and circulatory or respiratory failure (BTS 2010).[2]

Antibiotics

Before starting antibiotic treatment, a sputum sample should be sent for culture and sensitivity testing. Empirical antibiotic treatment is started immediately, without waiting for the result of microbiological testing which can take several days to achieve a result.[2]

Table 1: Selected risk factors for exacerbations and frequent exacerbations identified in the literature

	Risk of exacerbations	Risk of severe exacerbations
Bronchiectasis severity index[16]	Low-risk patients have 40% fewer exacerbations, severe patients have 70% more exacerbations, compared to moderate group	AUC 0.76-0.88 across derivation and validation studies to date
Prior severe exacerbations[16]	No direct analysis found but likely to correlate	HR 13.5 (95% CI 9.4-19.5), *P*<0.00001
MRC dyspnea score[16]	No direct analysis found	Score 1-3 (reference 2.0) IV HR 2.42 (95% CI 1.66-3.52) V HR 2.69 (95% CI 1.59-4.53)
Pseudomonas aeruginosa[16,24]	Mean difference 0.97 (95% CI 0.64-1.30), *P*<0.0001, *n*=3683 patients	OR 6.57 (95% CI 3.19-13.51), *P*<0.00001
Other bacteria[16,23]	Unclear. One study found *Haemophilus influenzae* was associated with fewer exacerbations	HR 1.48 (1.02-2.15), *n*=608 patients
Quantitative bacterial load[23]	Higher bacterial loads associated with more exacerbations over 12 months - OR 1.20, 95% CI 1.11-1.29, *P*<0.0001	OR 1.11 95% CI 1.01-1.21, *P*=0.02, *n*=385 patients
Radiological severity of disease[16,26]	>2 lobes involved associated with higher risk of having exacerbations versus no exacerbations OR 2.73, 95% CI 1.16-6.45	Reiff score HR 1.48 (1.02-2.15)
FEV1[16,26]	FEV_1<50% predicted associated with increased likelihood of having an exacerbation OR 4.03, 95% CI 1.75-9.26, *n*=460	FEV_1 >80%=1.0 (reference) FEV_1 50-80%=1.17 (0.74-1.85) FEV_1 30-49%=1.40 (0.68-2.85) FEV_1 <30%=1.52 (1.03-2.25)
Asthma[26]	Asthma associated with increased likelihood of having one or more exacerbations versus no exacerbations OR 2.6 95% CI 1.15-5.88, *P*=0.02	No data
Rhinosinusitis[34]	Increased risk during 1 year follow-up (*P*=0.02) *n*=160	Limited data
Gastroesophageal reflux[35]	Reflux defined using the Hull airway reflux questionnaire was independently associated with ≥3 exacerbations per year OR 7.7 95% 1.1-54, *P*=0.03	Limited data
Exhaled breath malondialdehyde[22]	Higher levels in patients with three or more exacerbations per year, *n*=152	Not studied
Sputum MMP-9[36,37]	Lower baseline levels associated with fewer exacerbation and longer time to first exacerbation, *n*=102	Not studied
Vitamin D deficiency[38]	Patients with severe Vitamin D deficiency had more exacerbations (*P*=0.04)	27.4% of patients with Vitamin D deficiency were hospitalized versus 19.7% with intermediate Vitamin D levels and 7.1% of sufficient patients, *P*=0.02
MBL deficiency[39]	MBL deficiency associated with mean 0.8/year increase in exacerbations (*P*<0.0001), *n*=470	Weak relationship between deficiency and severe exacerbations (*P*=0.03)
Socioeconomic deprivation[40]	See severe exacerbations	Higher frequency of individuals from low sociodemographics groups admitted to hospital compared to general population

OR: Odds ratio, CI: Confidence interval, HR: Hazard ratio, AUC: Area under the curve, MBL: Mannose-binding lectin, MMP-9: Matrix metalloproteinase-9, FEV_1: Forced expiratory volume in 1 s, MRC: Medical Research Council

The choice of antibiotic therapy should be guided by the patients' previous bacteriology, taking into all of the organisms that patients have grown in sputum over the previous 12 months. The choice of antibiotic is often guided as much by local/national customs as by microbiology, but in the UK, patients are most frequently treated with amoxicillin if there is no previous positive microbiology or doxycycline for those with penicillin allergy.[2] The only oral antibiotic option for patients colonized with *P. aeruginosa* is ciprofloxacin. The BTS guidelines provide a helpful table of suggested antibiotic treatments for different organisms.[2] Monotherapy is sufficient for the vast majority of outpatient exacerbations, and there is no evidence that giving combination antibiotic treatments in non-CF bronchiectasis results in either greater efficacy or reduced rates of resistance.

Consensus guidelines internationally suggest that bronchiectasis exacerbations should be treated with 14 days of antibiotic treatment.[2] This is based on experience in CF primarily, and there are no studies comparing 14 days treatment with shorter course regimes in bronchiectasis.

For more severe exacerbations where *P. aeruginosa* is the causative pathogen, combination treatment is frequently used. Examples such as a beta-lactam or antipseudomonal cephalosporin plus aminoglycoside are common. Bronchiectasis patients are often elderly with comorbidities including renal dysfunction, and this should be taken into account when choosing IV antibiotics and particularly with regard to aminoglycoside therapy.[44]

Adjuvant therapy in exacerbations

Bronchospasm is common during exacerbations in the presence of comorbid asthma/COPD or as a feature of bronchiectasis itself. Patients will therefore usually be treated with nebulized bronchodilators if bronchospasm

is present or advised to take short-acting bronchodilators via inhaler or spacer device if at home.[2] Corticosteroids have an established role in the management of asthma and COPD exacerbations and are used where these conditions are present with associated bronchospasm. The BTS recommends oral corticosteroids for acute exacerbations of bronchiectasis that are accompanied by wheezing suggestive of concomitant asthma.[2]

Patients should be encouraged to increase their airway clearance during exacerbations. This may involve simply performing techniques more frequently or using manual techniques where patients are unwell, fatigued, or finding their usual chest clearance insufficient. The involvement of a specialist chest physiotherapist is recommended where this is available.[2]

In severe exacerbations, oxygen therapy and ventilatory support can also be used. The BTS recommends a trial of noninvasive ventilation in patients with a respiratory acidosis (pH <7.35, H+ >45 nmol/L) secondary to an acute exacerbation of bronchiectasis, but excessive secretions are likely to limit its effectiveness.[2]

Assessment of treatment response

Murray *et al*. demonstrated significant improvements in sputum volume, inflammatory markers, and QoL without significant changes in FEV_1.[32]

Failure to respond to an antibiotic course should prompt a repeat culture and antibiotics should be modified guided by previous antibiotic sensitivity results.[2] As previously mentioned, if patient has a clinical failure after oral antibiotics, IV treatment is then recommended. Figure 1 summarizes some of the key issues in the management of bronchiectasis exacerbations.

PREVENTION OF EXACERBATIONS

Exacerbations cause significant morbidity and may also accelerate disease progression.[45] Therefore, a key objective of bronchiectasis treatment is to prevent exacerbations, Figure 2 resume some important issues in this topic

A few evidence-based treatments are available for the prevention and the management of bronchiectasis exacerbations:

- Vaccination (influenza and pneumococcal) is

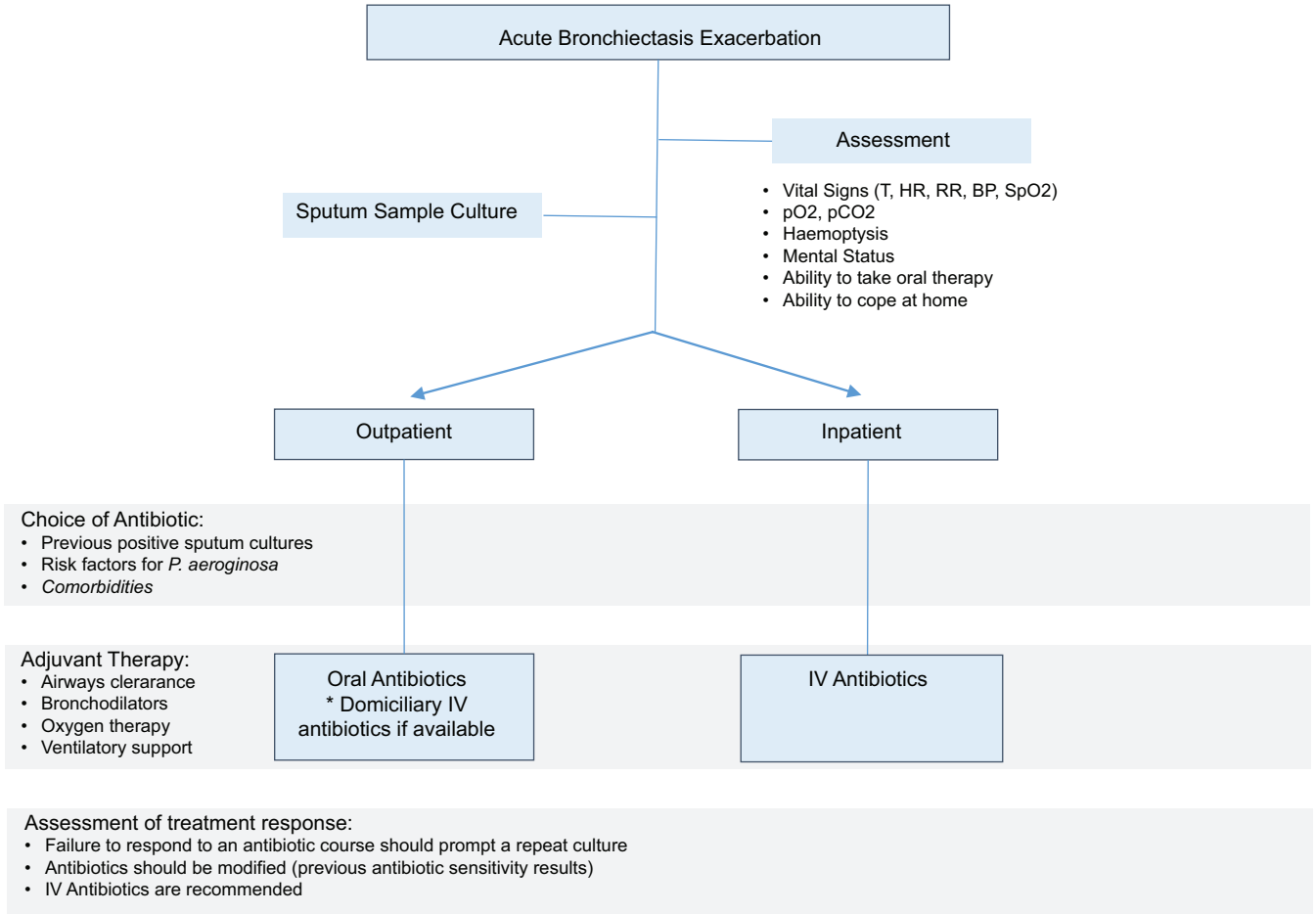

Figure 1: Management of acute exacerbations of bronchiectasis

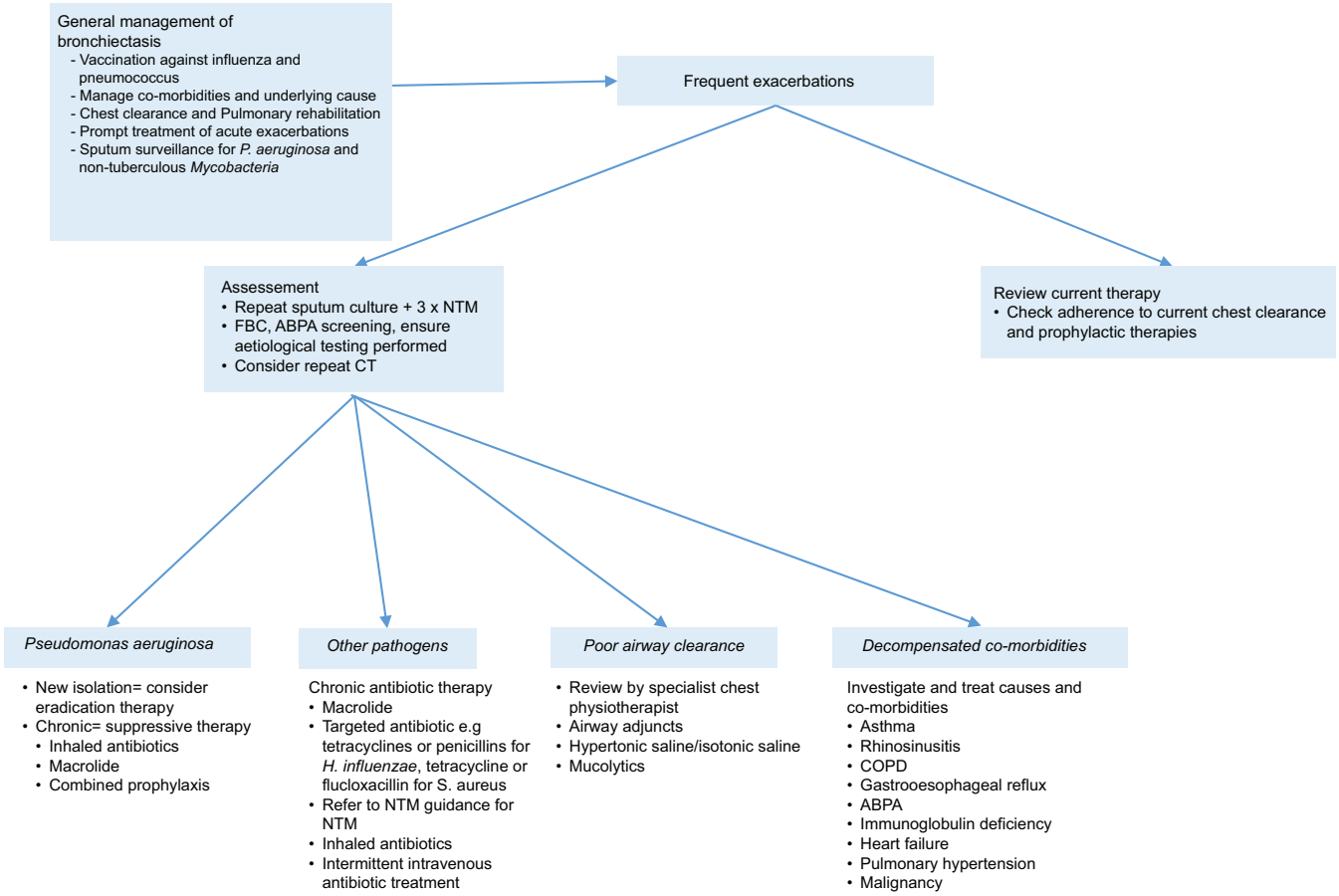

Figure 2: Prevention of exacerbations in stable patients with bronchiectasis

recommended in bronchiectasis patients by the BTS and *Spanish Society of Pneumology and Thoracic Surgery* although there is no evidence that vaccination reduces the exacerbation rate[2,15]

- Macrolide antibiotics are said to have anti-inflammatory and immunomodulatory properties in addition to their antibacterial properties. Three placebo-controlled randomized trials (EMBRACE, BAT, BLESS) show a significant decrease in event-based exacerbation rate and increase in time to the first exacerbation compared with placebo.[14,46,47] Benefits of macrolide treatment come with a considerable increase in macrolide-resistant pathogens and other side effects which demand judicious use of long-term macrolide therapy[46-49]
- Intermittent IV antibiotic treatment: In patients with frequent exacerbations despite prophylactic antibiotics and optimized treatments, 6–8 weekly IV antibiotic therapy has been shown to reduce exacerbations and improve QoL.[50] Nevertheless, there are significant resource implications and burden for patients with this approach
- Inhaled antibiotics are commonly used in CF bronchiectasis treatment to suppress *P. aeruginosa* and other pathogens. Despite the effectiveness of treatment with inhaled antibiotics in patients with CF has been demonstrated in several clinical trials, currently, there are insufficient large studies of patients with non-CF bronchiectasis and most of them are conflicting.[51-53] Most of the randomized clinical trials evaluate inhaled antimicrobial agents included bronchiectasis patients colonized with *P. aeruginosa* and used different types of antibiotics (colistin, tobramycin, gentamicin, or ciprofloxacin). Three distinct trials using aztreonam, gentamicin, and ciprofloxacin, which did not specifically require *P. aeruginosa* colonization for inclusion, demonstrated bacterial load reduction in the airways, but this effect does not correspond with improvement in clinical endpoints.[12] The largest trial ($n = 500$) of inhaled aztreonam in bronchiectasis patients –85% of whom were *P. aeruginosa* colonized – failed to demonstrate reduced exacerbation rates or improved QoL. Other authors report prolonged time to exacerbation and improved health-related QoL.[51] Nevertheless, inhaled antibiotics are widely used in clinical practice and appear to have benefits in selected patients. The main adverse effect is bronchospasm
- Targeted antibiotics: Trials of long-term penicillins and tetracyclines from the 1980's or earlier suggest benefits in patients with bronchiectasis, but further studies are needed.[54] Long-term penicillins and tetracyclines are

used either as alternatives in patients with macrolide intolerance or for targeted treatment of specific pathogens
- Airway clearance techniques are recommended for patients with stable bronchiectasis to optimize the airway clearance leading to decrease sputum expectoration, symptoms, and exacerbation rate and also increase lung function, gas exchange, and QoL.[55] Specific techniques used in airway clearance include:
  - Breathing exercises such as the active cycle of breathing technique
  - Gravity-assisted drainage
  - Autogenic drainage
  - Manual techniques such as clapping
  - Forced expiratory technique
  - Application of positive expiratory pressure devices
- Adherence is a major problem, particularly when patients feel well, and hence, it is important to tailor the techniques to the patient's lifestyle, to emphasize the importance of airway clearance at each visit, and to discuss adherence[56]
- Hypertonic saline (HTS) 4–7% is reported to improve hydration of the airway surface and the rheology and transportability of sputum. Inhalation of HTS has short-term positive effects on airways clearance in bronchiectasis; however, its long-term effects are unknown. One trial showed no benefits compared to isotonic saline over 12 months[57]
- Pulmonary rehabilitation: Lee *et al*. showed a reduction in exacerbations over 12 months in patients randomized to exercise training, suggesting that pulmonary rehabilitation may play a role in reducing exacerbations.[58] All patients with significant breathlessness should be considered for exercise treatments.

CONCLUSIONS

Prompt appropriate treatment of exacerbations will reduce the impact on patients and improve QoL. Prevention of exacerbations is important to prevent disease progression and deterioration in QoL.

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Conflicts of interest

There are no conflicts of interest.

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