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The European Respiratory Society (ERS) Guidelines for the Management of Adult Bronchiectasis

Eva Polverino[1], Pieter C Goeminne[2], Melissa J McDonnell[3], Stefano Aliberti[4], Sara E Marshall[5], Michael R Loebinger[6], Marlene Murris[7], Rafael Cantón[8], Antoni Torres[9], Katerina Dimakou[10] Anthony De Soyza[11], Adam T Hill[12], Charles S Haworth[13], Montserrat Vendrell[14], Felix C. Ringshausen[15], Dragan Subotic[16], Robert Wilson[6], Jordi Vilaró[17], Bjorn Stallberg[18], Tobias Welte[15], Gernot Rohde[19], Francesco Blasi[4], Stuart Elborn[6-20], Marta Almagro[21], Alan Timothy[21], Thomas Ruddy[21], Thomy Tonia[22], David Rigau[23], James D Chalmers[24].

Affiliations

[1] Servei de Pneumologia, Hospital Universitari Vall d'Hebron (HUVH), Institut de Recerca Vall d'Hebron (VHIR); Fundación Clínic, Hospital Clínic de Barcelona, Universitat de Barcelona, IDIBAPS, CIBERES Barcelona, España.

[2] Department of Respiratory Medicine, AZ Nikolaas, Sint-Niklaas, Belgium; Department of Respiratory Medicine, UZ Leuven, Leuven, Belgium.

[3] Department of Respiratory Medicine, Galway University Hospitals, Galway, Ireland; Lung Biology Group, National University of Ireland, Galway, Ireland; Institute of Cell and Molecular Biology, Newcastle University, Newcastle upon Tyne, UK.

[4] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Internal Medicine Department, Respiratory Unit and Adult Cystic Fibrosis Center Fondazione IRCCS Cà Granda Ospedale Maggiore Policlinico Milan, Italy.

[5] Department of Clinical Research, Immunology and Physiological Sciences, Wellcome, London

[6] Host Defence Unit, Royal Brompton Hospital, Imperial College, London, UK

[7] Service de Pneumologie, Hôpital Larrey, CHU de Toulouse, Toulouse, France

[8] Servicio de Microbiología, Hospital Universitario Ramón y Cajal and Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Madrid, Spain

[9] Servei de Pneumologia, Hospital Clínic de Barcelona, Universitat de Barcelona, IDIBAPS, CIBERES Barcelona, España

[10] 5th Pulmonary Department, "Sotiria" Chest Hospital, Athens, Greece

[11] Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, UK; Bronchiectasis Service, Freeman Hospital, Newcastle upon Tyne, UK

[12] Department of Respiratory Medicine, Royal Infirmary and University of Edinburgh, UK

[13] Cambridge Centre for Lung Infection, Papworth Hospital, Cambridge, UK

[14] Bronchiectasis Group, Girona Biomedical Research Institute (IDIBGI), Dr Trueta University Hospital, Girona, Spain

[15] Department of Respiratory Medicine, Hannover Medical School, Member of the German Centre for Lung Research, Hannover, Germany

[16] Clinic for Thoracic Surgery - Clinical Centre of Serbia, University of Belgrade, Belgrade, Serbia

[17] FCS Blanquerna. Physical Activity and Health Group, Universitat Ramon Llull, Barcelona, Spain.

[18] Department of Public Health and Caring Science, Family Medicine and Preventive Medicine, Uppsala University, Uppsala, Sweden

[19] Department of Respiratory Medicine, Maastricht University Medical Center, Maastricht, The Netherlands

[20] Queen's University Belfast

[21] European Lung Foundation (ELF)/EMBARC bronchiectasis patient advisory group, Sheffield, UK

[22] Institute of Social and Preventive Medicine, University of Bern, Switzerland

[23] Iberoamerican Cochrane Center, Barcelona, Spain

[24] College of Medicine, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK

Correspondence details:

James D Chalmers, Scottish Centre for Respiratory Research, Ninewells Hospital and Medical School, Dundee, DD1 9SY

Telephone +441382383642, e-mail: jchalmers@dundee.ac.uk

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ABSTRACT

Bronchiectasis in adults is a chronic disorder associated with poor quality of life and frequent exacerbations in many patients. There have been no previous international guidelines.

The European Respiratory Society Guidelines for the Management of Adult Bronchiectasis describe the appropriate investigation and treatment strategies determined by a systematic review of the literature.

A multidisciplinary group representing respiratory medicine, microbiology, physiotherapy, thoracic surgery, primary care, methodology and patients considered the most relevant clinical questions (for both clinicians and patients) related to management of bronchiectasis. Nine key clinical questions were generated and a systematic review was conducted to identify published systematic reviews, randomized clinical trials and observational studies that answered these questions. We used the GRADE approach to define the quality of the evidence and the level of recommendations. The resulting guideline addresses the investigation of underlying causes of bronchiectasis, treatment of exacerbations, pathogen eradication, long term antibiotic treatment, anti-inflammatories, mucoactive drugs, bronchodilators, surgical treatment and respiratory physiotherapy.

These recommendations can be used to benchmark quality of care for people with bronchiectasis across Europe and to improve outcomes.

Scope and objectives

This guideline provides evidence-based recommendations for the management of adult patients with bronchiectasis. It only applies to patients with clinically significant bronchiectasis, defined by the presence of both permanent bronchial dilatation on CT scanning and the clinical syndrome of cough, sputum production and/or recurrent respiratory infections. Radiological bronchiectasis may be evident in healthy asymptomatic individuals, particularly in the elderly[1] or may occur, for example, due to traction in interstitial lung disease. Such radiological bronchiectasis without clinical symptoms are not addressed in this guideline. The following conditions are also excluded: cystic fibrosis (CF) bronchiectasis, which has a distinct pathophysiology and treatment pathway, children with bronchiectasis, treatment of primary immunodeficiencies and non-tuberculous mycobacteria, where disease specific therapy is indicated. The majority of these clinical issues are addressed in other guidelines.

This guideline document does not address clinical and radiological diagnosis of bronchiectasis but rather focuses on key questions in management. Areas such as smoking cessation, nutrition, influenza and pneumococcal vaccination among other aspects of general management are not specifically addressed in this document. Readers are referred to relevance guidelines and national policies. A guideline document cannot address the full complexity of a disease such as bronchiectasis, hence all recommendations should be interpreted taking into account the clinical circumstances and patients' perceptions, values and preferences.

Table 1 provides a framework to understand the recommendations made in this document[2, 3].

Target group	Strong recommendations*	Conditional (weak) recommendations
Patients	All or almost all informed people would choose the recommended choice for or against an intervention.	Most informed people would choose the recommended course of action, but a substantial number would not.
Clinicians	Most patients should receive the recommended course of action	Recognize that different choices will be appropriate for different patients. Clinicians and other health care providers need to devote more time to the process

		of shared decision making by which they ensure that the informed choice reflects individual values and preferences; decision aids and shared decision making are particularly useful
Policy makers	The recommendation can be adopted as a policy in most situations	Policy making will require substantial debate and involvement of many stakeholders

GRADE, Grades of Recommendation, Assessment, Development and Evaluation.

*Strong recommendations based on high quality evidence will apply to most patients for whom these recommendations are made, but they may not apply to all patients in all conditions; no recommendation can take into account all of the unique features of individual patients and clinical circumstances.

The target audience for this guideline are all stakeholders involved bronchiectasis care. This includes specialists in respiratory medicine, infectious diseases, clinical microbiology, general internists, specialists in thoracic surgery, primary care physicians, pharmacists, respiratory physiotherapists, specialist nurses, regulatory authorities, pharmaceutical companies and policy makers. The guideline is also to inform people with BE to help them in discussion with their care teams to enable them to access appropriate care.

Introduction

Bronchiectasis is a chronic respiratory disease characterised by a clinical syndrome of cough, sputum production and bronchial infection, and radiologically by abnormal and permanent dilatation of the bronchi. The objectives of treatment in bronchiectasis are to prevent exacerbations, reduce symptoms, improve quality of life and stop disease progression. Cough and sputum production, along with breathlessness are the most frequent symptoms but rhino-sinusitis, fatigue, haemoptysis and thoracic pain are also common[4]. Quality of life impairment in bronchiectasis is equivalent in terms of scores on the St. Georges respiratory questionnaire (SGRQ) to severe COPD, idiopathic pulmonary fibrosis and other disabling respiratory diseases[5, 6].

Exacerbations of bronchiectasis are key targets for therapy as they are major determinants of healthcare costs. They are associated with increased airways and systemic inflammation[7]and progressive lung damage[8, 9]. In addition, more severe and more frequent exacerbations are associated

with worse quality of life, daily symptoms[10], lung function decline[11], and mortality [9]. Consequently, the majority of therapeutic interventions are aimed at reducing exacerbations. Despite current treatment approaches, European registry data shows that approximately 50% of European bronchiectasis patients have 2 or more exacerbations per year and one third require at least 1 hospitalization per year[12].

Our understanding of what causes symptoms and exacerbations is based on the vicious cycle concept, with key components of the disease being chronic bronchial infection, inflammation, impaired mucociliary clearance and structural lung damage. Treatment is primarily based on the principles of preventing or suppressing acute and chronic bronchial infection, improving mucociliary clearance and reducing the impact of structural lung disease (Figure 1).

Chronic airways infection, most frequently with *Haemophilus influenzae* and *Pseudomonas aeruginosa* and less frequently with *Moraxella catarrhalis, Staphylococcus aureus* and *Enterobacteriaceae*, stimulate and sustain lung inflammation. Persistent isolation of these organisms in sputum or bronchoalveolar lavage is associated with an increased frequency of exacerbations, worse quality of life and increased mortality[13, 14]. This is particularly the case with *P. aeruginosa* infection. A systematic review of observational studies identified that *P. aeruginosa* infection is associated with a 3-fold increase in mortality risk, an almost 7-fold increase in risk of hospital admission and an average of 1 additional exacerbation per patient per year[15].

Inflammation in bronchiectasis is primarily neutrophilic and closely linked to persistent bacterial infection. Excessive neutrophilic inflammation is linked to an increased frequency of exacerbations and rapid lung function decline through degradation of airway elastin among other mechanisms [16-19]. The available data also support a role for cell-mediated immunity, specifically T-cells in the pathophysiology of bronchiectasis but the role of other inflammatory cells is less clear[17].

Mucociliary clearance is impaired by the impact of structural bronchiectasis, airway dehydration, excess mucus volume and viscosity. More than 70% of bronchiectasis patients expectorate sputum daily with highly variable sputum volumes. Treatment aims to prevent mucus stasis and the associated mucus plugging, airflow obstruction and progressive lung damage[20].

Structural lung disease includes bronchial dilatation, bronchial wall thickening, and mucus plugging as well as small airways disease and emphysema. More than 50% of patients have airflow obstruction, but restrictive, mixed ventilatory pattern and preserved lung function are also frequently observed. Breathlessness is due to the impact of airflow obstruction, impaired gas transfer, exercise deconditioning and the impact of co-morbidities[21-24]. Breathlessness is one of the strongest predictors of mortality[9, 14]. Therapies may aim to treat airflow obstruction (e.g. bronchodilators), to improve exercise

capacity (pulmonary rehabilitation), or to remove poorly functioning or diseased lung (e.g. surgery).

Bronchiectasis has long been a neglected disease. The prevalence of bronchiectasis has been estimated at 53 to 566 cases per 100,000 inhabitants. Prevalence increases with age and female gender [25-29]. *Quint et al.* described that age-adjusted mortality rate for bronchiectasis was 1437.7 per 100,000.[28] Several longitudinal studies have described up to a 30% mortality at 1-year follow-up after suffering an exacerbation [30,31], particularly in the presence of COPD[32].

The economic burden of this disease has been estimated to be similar to COPD; this increases with disease severity, hospitalizations, ICU, and use of inhaled antibiotics [25, 26, 30, 33-35]. No therapies are currently specifically licensed by regulatory authorities in Europe or the United States for the treatment of bronchiectasis. Historically, treatment has been extrapolated from the management of CF bronchiectasis, but randomized clinical trials and clinical experience has often demonstrated that treatment responses are different and that specific guidance for bronchiectasis not due to CF is necessary [36, 37].

National guidelines are available in Europe: the Spanish guidelines (SEPAR) were published in 2008 [38] and the British Thoracic Society guidelines were published in 2010 [39]. Aspects of management of acute exacerbations in bronchiectasis were addressed in the ERS/ESCMID lower respiratory tract infections guidelines published in 2011[40]. However, to date, there are no international guidelines for the management of adult bronchiectasis published and no national guidelines published in Europe in the past 5 years.

METHODS

This guideline was developed by a European Respiratory Society Bronchiectasis Task Force chaired by Dr Eva Polverino (Spain) and Dr James D Chalmers (UK). The task force included specialists in respiratory medicine with recognized expertise in the management of patients with lung infections, as well as a microbiologist, an immunologist, a physiotherapist, a general practitioner, a thoracic surgeon, 3 patient representatives from the EMBARC/European Lung Foundation (ELF) bronchiectasis patient advisory group and two ERS methodologists.

The guideline panel held four face-to-face meetings, beginning in January 2015. The most relevant clinical questions on the management of bronchiectasis in adults (for both clinicians and patients) were debated. A total of 9 clinical questions were formulated using the PICO format (PICO: Patients, Intervention, Comparison, Outcomes) and systematic reviews were conducted to answer these specific questions, until September 2016 when the final guideline recommendations were discussed and agreed. Regular teleconferences and discussions via e-mail around individual topics were held. The patient rep-

resentatives were actively involved in all discussions as full members of the guideline committee, provided input into the final recommendations and will be involved in developing a lay version of the guideline.

Disclosure of potential conflicts of interest

Committee members disclosed all potential conflicts of interest according to ERS policy. Conflicted members were asked to abstain from discussions and voting on recommendations in which they were considered to have potential conflicts. Compliance with the conflict of interest policy was monitored by the chairs. The methodologists were non-voting members of the panel.

Systematic review

An experienced external librarian designed and ran a search strategy using MeSH terms and keywords for each clinical question, in collaboration with the methodologists. More details of the search strategy are shown in the online supplemental material. The search retrieved 3,038 records; after removal of duplicates and exclusion of citations that did not meet the established inclusion criteria, a total of 48 references were included in the evidence summaries (Figure 2; online material).

Assessment of the level of evidence and degree of recommendations

The panel selected outcomes of interest for each clinical question a priori, based on their relative importance to adult patients with bronchiectasis and to clinical decision making (online material).

We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations[41]. Recommendations are graded as strong or conditional after considering the quality of the evidence, the balance of desirable and undesirable consequences of compared management options, the assumptions about the relative importance of outcomes, the implications for resource use, and the acceptability and feasibility of implementation[42].

Evidence summaries of findings (SoF tables) and Evidence to Decisions (EtD) frameworks were generated for each clinical question [43] (online material). Based on these formats, the panel formulated the clinical recommendations and decided on their strength by consensus and, if required, by voting. Following the GRADE approach, strong recommendations are worded as "we recommend", while conditional recommendations are worded as "we suggest".

Table 2 SUMMARY OF PICO QUESTIONS AND RECOMMENDATIONS

QUESTION	TITLE	RECOMMENDATIONS
Question 1	Is the application of current SEPAR/BTS recommendations about aetiological testing panel of bronchiectasis beneficial for their clinical management in comparison with no standardized aetiological testing?	We suggest the minimum bundle of aetiological tests in adults with a new diagnosis of bronchiectasis *(conditional recommendation, very low quality of evidence)* is: 1. Differential blood count 2. Serum immunoglobulins (total IgG, IgA, IgM) 3. Testing for allergic bronchopulmonary aspergillosis (ABPA)

		It is expected that sputum culture is undertaken for monitoring purposes of bacterial infection. Mycobacterial culture may be helpful in selected cases where non-tuberculous mycobacteria (NTM) are suspected as an aetiological cause of bronchiectasis. Additional tests may be appropriate in response to specific clinical features, or in patients with severe or rapidly progressive disease.
Question 2	Are courses of 14-21 days of systemic antibiotic therapy compared to shorter courses (<14 days) beneficial for treating adult BE patients with an acute exacerbation?	We suggest acute exacerbations of bronchiectasis should be treated with 14 days of antibiotics (*conditional recommendation, very low quality of evidence*). It is possible that shorter or longer courses of antibiotics may be appropriate in some cases, depending on specific clinical conditions (such as exacerbation severity, patient' response to treatment, or microbiology)
Question 3	Is an eradication treatment beneficial for treating BE patients with a new isolate of a potentially pathogenic microorganism in comparison to no eradication treatment?	- We suggest that adults with bronchiectasis with a new isolation of *P. aeruginosa* should be offered eradication antibiotic treatment (*conditional recommendation, very low quality of evidence*). - We suggest not offering eradication antibiotic treatment to adults with bronchiectasis following new isolation of pathogens other than *P. aeruginosa*

		(*conditional recommendation, very low quality of evidence*)
Question 4	Is long-term (≥ 3 months) anti-inflammatory treatment compared to no treatment beneficial for treating adult bronchiectasis patients?	- We suggest not offering treatment with inhaled corticosteroids to adults with bronchiectasis (*conditional recommendation, low quality of evidence*). - We recommend not offering statins for the treatment of bronchiectasis (*strong recommendation, low quality of evidence*). - We suggest that the diagnosis of bronchiectasis should not affect the use of inhaled corticosteroids in patients with comorbid asthma or COPD (*Best practice advice, indirect evidence*).
Question 5	Is long-term antibiotic treatment (≥3 months) compared to no treatment beneficial for treating adult bronchiectasis patients?	We suggest offering long-term antibiotic treatment for adults with bronchiectasis who have three or more exacerbations per year (*conditional recommendation, moderate quality evidence*). All subsequent recommendations refer to patients with three or more exacerbations per year. - We suggest long-term treatment with an inhaled antibiotic for adults with bronchiectasis and chronic *P. aeruginosa* infection (*conditional recommendation, moderate quality evidence*).

		- We suggest macrolides (azithromycin, erythromycin) for adults with bronchiectasis and chronic *P. aeruginosa* infection in whom an inhaled antibiotic is contraindicated, not tolerated or not feasible (*conditional recommendation, low quality evidence*). - We suggest macrolides (azithromycin, erythromycin) in addition to or in place of an inhaled antibiotic, for adults with bronchiectasis and chronic *P. aeruginosa* infection who have a high exacerbation frequency despite taking an inhaled antibiotic (*conditional recommendation, low quality evidence*). - We suggest long-term macrolides (azithromycin, erythromycin) for adults with bronchiectasis not infected with *P. aeruginosa* (*conditional recommendation, moderate quality evidence*). - We suggest long-term treatment with an oral antibiotic (choice based on antibiotic susceptibility and patient tolerance) for adults with bronchiectasis not infected with *P. aeruginosa* in whom macrolides are contraindicated, not

		tolerated or ineffective (*conditional recommendation, low quality evidence*).
		- We suggest long-term treatment with an inhaled antibiotic for adults with bronchiectasis not infected with *P. aeruginosa* in whom oral antibiotic prophylaxis is contraindicated, not tolerated or ineffective (*conditional recommendation, low quality of evidence*).
		- Long-term antibiotic therapy should be considered only after optimisation of general aspects of bronchiectasis management (airway clearance and treating modifiable underlying causes).
Question 6	Is long-term mucoactive treatment (≥3 months) compared to no treatment beneficial for treating adult bronchiectasis patients?	We suggest offering long-term mucoactive treatment (≥ 3 months) in adult patients with bronchiectasis who have difficulty in expectorating sputum and poor quality of life and where standard airway clearance techniques have failed to control symptoms (*weak recommendation, low quality evidence*). We recommend not offering recombinant human DNase to adult patients with bronchiectasis (*strong recommendation, moderate quality evidence*)

| Question 7 | Is long-term bronchodilator treatment (≥3 months) compared to no treatment beneficial for adult bronchiectasis patients? | We suggest not routinely offering long-acting bronchodilators for adult patients with bronchiectasis (*conditional recommendation, very low quality of evidence*)

We suggest offering long acting bronchodilators for patients with significant breathlessness on an individual basis (*weak recommendation, very low quality of evidence*).

We suggest using bronchodilators before physiotherapy, including inhaled mucoactive drugs, as well as before inhaled antibiotics, in order to increase tolerability and optimize pulmonary deposition in diseased areas of the lungs (good practice point, indirect evidence).
We suggest that the diagnosis of bronchiectasis should not affect the use of long acting bronchodilators in patients with comorbid asthma or COPD [44][45] (*good practice point, indirect evidence*). |
| Question 8 | Are surgical interventions more beneficial compared to standard (non-surgical) treatment for adult bronchiectasis patients? | We suggest not offering surgical treatments for adult patients with bronchiectasis with the exception of patients with localised disease and a high exacerbation frequency despite optimisation of all other aspects of their bronchiectasis management (*weak recommendation, very low quality of evidence*). |

Question 9	Is regular physiotherapy (airway clearance and/or pulmonary rehabilitation) more beneficial than control (no physiotherapy) in adult bronchiectasis patients?	- We suggest that patients with chronic productive cough or difficulty to expectorate sputum should be taught an airways clearance technique (ACT) by a trained respiratory physiotherapist to perform once or twice daily (*weak recommendation, low quality of evidence*). - We recommend that adult patients with bronchiectasis and impaired exercise capacity should participate in a pulmonary rehabilitiation program and take regular exercise. All interventions should be tailored to the patient's symptoms, physical capability and disease characteristics (*strong recommendation, high quality of evidence).*

Question 1: **Is the application of current SEPAR/BTS recommendations about aetiological testing panel of bronchiectasis beneficial for their clinical management in comparison with no standardized aetiological testing?**

Recommendations

We suggest the minimum bundle of aetiological tests in adults with a new diagnosis of bronchiectasis *(conditional recommendation, very low quality of evidence)* is:

- Differential blood count
- Serum immunoglobulins (total IgG, IgA, IgM)
- Testing for allergic bronchopulmonary aspergillosis (ABPA)

It is expected that sputum culture is undertaken for monitoring purposes of bacterial infection. Mycobacterial culture may be helpful in selected cases where non-tuberculous mycobacteria (NTM) are suspected as an aetiological cause of bronchiectasis. Additional tests may be appropriate in response to specific clinical features, or in patients with severe or rapidly progressive disease.

Summary of the evidence

The SEPAR and BTS guidelines have previously recommended a routine "bundle" of tests at diagnosis to identify possible underlying causes of bronchiectasis[38][39]. Our systematic review identified no publications which directly addressed whether routine aetiological investigation protocols provide benefit compared to clinically driven investigations or no testing. Four observational studies were identified which describe the percentage of adult patients (7%-37%) whose management changed following investigation of aetiology while no other relevant outcomes were reported[46-49].

Justification of the recommendation

Measurement of circulating white cell count and differential is suggested in all patients. The presence of lymphopaenia or neutropaenia may suggest primary or secondary immune deficiency, while lymphocytosis may suggest secondary immune deficiency as a consequence of haematological malignancy. Serum IgA, IgM, IgG are generally tested together, and we have considered them jointly. Low IgG, with or without low IgM or low IgA may indicates a defective antibody production that is an important modifiable cause of bronchiectasis, and 2-8% of patients with bronchiectasis have common variable immune deficiency[46-48]. Importantly, in these cases immunoglobulin replacement treatment can result in significant improvement in short and long-term outcomes. The cost of serum immunoglobulin testing is low and testing is readily available.

The geographic distribution of ABPA is thought to be variable, but establishing diagnosis alters management[49]. Hence the panel advises routine screening of all patients for ABPA at diagnosis. The generally recommended screening tests for ABPA are total serum IgE, specific IgG to *Aspergillus*, and specific IgE to *Aspergillus* or, as an alternative, skin prick tests to *Aspergillus*[50, 51].

A range of other tests may be appropriate in specific circumstances. In patients with radiological features of NTM or clinical features such as weight loss, haemoptysis, rapid deterioration or symptoms non-responsive to standard therapy, three sequential daily sputum cultures for mycobacterial cultures or a single bronchoalveolar lavage (BAL) should be considered[52]. Some authorities recommend measuring antibody responses to *S. pneumoniae* 23 valent polysaccharide vaccine (PPV23) in order to identify individuals with specific polysaccharide antibody deficiency[38][39]. Failure to make an antibody response to PPV23 (4-fold increase in titre at 4-6 weeks) may suggest a defect in carbohydrate antigen responses. However, due to the large variability in individual antibody response to PPV23 and in testing protocols, this evaluation should not be performed without specialist support. Testing for CF with measurement of sweat chloride, other biomarkers of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR)-mediated chloride ion transport and CFTR gene mutation analysis should be considered in young adults or with specific clinical features of CF such as upper lobe predominance of bronchiectasis on chest CT, the presence of nasal polyposis and/or chronic rhinosinusitis, recurrent pancreatitis, male primary infertility and/or malabsorption. Testing for primary ciliary dyskinesia with nasal nitric oxide, high-speed video analysis, transmission electron microscopy, immunofluorescence and/or genetic testing should be considered for patients with several of the following features: persistent wet cough since childhood, situs anomalies, congenital cardiac defects, nasal polyposis and/or chronic rhinosinusitis, chronic middle ear disease with or without hearing loss, a history of neonatal respiratory distress or neonatal intensive care admittance in term infants. Refer to the ERS guidelines for the diagnosis of PCD for more information[53]. The presence of basal emphysema or early onset airflow obstruction could suggest the need to exclude alpha1-antitrypsin deficiency. There are a wide range of other causes of bronchiectasis many of which can be identified by history, physical examination and CT scanning. We do not recommend routine testing of autoantibodies to screen for connective tissue disease, but evidence of connective tissue disease should be sought by history and physical examination.

The suggested bundle is justified by the fact that, despite the lack of strong evidence, selected tests can considerably alter the clinical management of bronchiectasis by indicating specific therapeutic interventions such as immunoglobulin replacement, corticosteroids, or antifungal treatment. These interventions imply significant potential benefits for some individuals, and minimal undesirable effects from testing for others. The patient advisory group reported that patients placed a high value on identifying the underlying cause of bronchiectasis.

Implementation considerations

The standard tests recommended in this bundle should be available in the majority of healthcare systems and should not present major implementation issues.

Question 2: **Are courses of 14-21 days of systemic antibiotic therapy compared to shorter courses (<14 days) beneficial for treating adult bronchiectasis patients with an acute exacerbation?**

Recommendation

We suggest acute exacerbations of bronchiectasis should be treated with 14 days of antibiotics (*conditional recommendation, very low quality of evidence*).

Summary of the evidence

Bronchiectasis patients are typically given prolonged courses of antibiotics of 14 days' duration for infective exacerbations. This recommendation is given in previous guidelines for bronchiectasis [38,39]. It is based on expert consensus and studies that documented good clinical outcomes with such treatment regimens. However, the evidence base for this duration is poor.

The published literature was assessed as to whether shorter (<14 days) courses of antibiotics would be as clinically effective or be associated with any benefit or harm compared to 14-21 days of therapy. There was no direct evidence of benefit favouring either 14-21 days or shorter courses of antibiotic therapy. The only data comes from an indirect comparison of response at day 7 vs. day 14 in 53 patients, all receiving ciprofloxacin (with or without inhaled tobramycin) for 14 days. After pooling both study arms, bacterial load (MD: +0.23 cfu/ml higher; 95%CI: -1.55 to +2.01) and FEV1 (MD: +0.01 Litres; 95%CI: -0.51 to +0.53) were similar at 7 and 14 days with wide confidence intervals including both benefit and harm. No data was available for clinical outcome such as subsequent quality of life and exacerbations [54][online material]

Data from other studies. Some authors have shown a favourable impact of 14 days of antibiotics for treatment of a bronchiectasis exacerbation. One study of 32 exacerbations treated with 14 days of intravenous antibiotics demonstrated significant improvement in 24-hour sputum volume, bacterial clearance, C-reactive protein, incremental walk test and SGRQ but no improvement in spirometry[55]. A further study of 34 patients treated with intravenous antibiotics for 14 days demonstrated a reduction in sputum bacterial load and markers of airway inflammation after antibiotic treatment[56].

Justification of the recommendations

In the absence of any direct data comparing longer and shorter courses of antibiotics, we suggest continuing the usual practice of treating acute exacerbations of bronchiectasis with 14 days of antibiotics on the basis of the patient's prior microbiology testing and the severity of the exacerbation. Patients have diverse views on the duration of antibiotics for exacerbations, with some preferring longer courses, and other patients wishing to use shorter courses if possible.

Implementation considerations

It is possible that shorter courses of antibiotics may be appropriate in some cases. The Task Force panel suggests that mild exacerbations, exacerbations in mild patients, those associated with pathogens more sensitive to antibiotics (e.g. *S. pneumoniae*), or patients with a rapid return to baseline state may benefit from shorter courses, however evidence supporting shorter course treatment is lacking Otherwise, in patients with lack of recovery by 14 days of antibiotic therapy we suggest re-evaluation of the patients clinical condition and a new microbiological investigation. Sending a sputum sample at the start of an exacerbation is helpful to guide choice of antibiotics in the event of inadequate response to initial therapy. Due to variations in antibiotic use and healthcare practices across Europe, we do not address choice of specific antibiotics, or the role of combination vs. monotherapy in this guideline.

Further research studies assessing the optimal duration of antibiotics are recommended.

Question 3: **Is eradication treatment beneficial for treating ronchiectasis patients with a new isolate of a potentially pathogenic microorganism in comparison to no eradication treatment?**

Recommendations

We suggest that adults with bronchiectasis with a new isolation of *P. aeruginosa* should be offered eradication antibiotic treatment (*conditional recommendation, very low quality of evidence*).

We suggest not offering eradication antibiotic treatment to adults with bronchiectasis following new isolation of pathogens other than *P. aeruginosa* (*conditional recommendation, very low quality of evidence*)

Summary of the evidence

Eradication treatment refers to any antibiotic treatment given with the express intention of achieving complete clearance of the pathogen from the airway. In bronchiectasis, eradication treatment regimens vary, but there is some evidence suggesting that a regimen including a nebulized antibiotic achieves greater rates of clearance and clinical benefits than intravenous treatment alone[57].

Chronic airway infection in adult patients with bronchiectasis is frequent and usually associated with worse outcomes such as more exacerbations and poorer quality of life[15, 58]. Definitions of chronic airway infection in bronchiectasis are not established but a systematic review identified that the most frequent definition used in bronchiectasis studies is 2 or more isolates of the same organism at least 3 months apart in one year[15]. Unfortunately, in patients with persistent infections, there is little evidence about the beneficial effects of pathogen eradication beyond *P. aeruginosa.*

We could not identify any randomised controlled trial (RCT) directly addressing the question. Therefore we included two studies that investigated whether eradication treatment in adult patients with bronchiectasis improved clinical outcomes compared to the patients own baseline[59, 60]. Pooled analysis provides some evidence of the potential benefits of *P. aeruginosa* eradication in terms of negative sputum samples, frequency of subsequentexacerbations and quality of life but the evidence is indirect and considered of low quality.

In particular, the retrospective observational study of White *et al*. analysed different eradication treatment regimens: IV antibiotics (12 cases), IV antibiotics followed by inhaled antibiotics (13 cases), and oral ciprofloxacin alone. 25 patients across all groups received 3 months of inhaled colistin. Initial clearance rate from sputum was 80%, but 54% of all patients remained *P. aeruginosa* free at follow-up and the exacerbation rate fell from 3.93 to 2.09 per year after the eradication treatment. In addition, two thirds of patients experienced clinical improvement although lung function remained unchanged.

Orriols *et al.* performed a 15-month single-masked, RCT in 35 patients with early *P. aeruginosa* infection[57]. These patients received initial therapy with IV ceftazidime or tobramycin followed by three

months of 300mg of nebulised tobramycin BD or placebo. At the end of follow-up (12 months), 54% of patients were free of *P. aeruginosa* in the tobramycin group vs. 29% in the placebo group. Despite some potential methodological limitations, this study showed that the median time to recurrence of *P. aeruginosa* was longer in the treatment arm compared to placebo and numbers of exacerbations and hospital admissions were lower in the nebulised tobramycin group. The impact of eradication treatments on the development of antibiotic resistance was not extensively studied. This study had no control group and so is limited in terms of informing whether eradication is effective.

There is no clear evidence to support one regimen over another, and therefore Figure 3 illustrates some commonly used regimes.

Justification of the recommendation

The poor clinical outcomes associated with chronic *P. aeruginosa* infection, the data from one observational study and the clinical experience in CF suggests that *P. aeruginosa* eradication may positively influence important clinical outcomes including exacerbation frequency.

There is no evidence to support eradication of organisms other than *P. aeruginosa* and in organisms that are not so clearly associated with poorer outcomes, the risk-benefit ratio is less in favour of eradication treatment.

Implementation considerations

Identification of new isolates of *P. aeruginosa* requires regular sputum surveillance which has resource implications. We suggest as a minimum that patients should have a sputum sample sent when clinically stable once per year. In circumstances where the date of acquisition of *P. aeruginosa* is uncertain, a clinical judgement must be made on the likely success or otherwise of an eradication attempt. This guideline does not address attempted eradication of chronic *P. aeruginosa* infection, where the infection has been present for many years, as this is thought unlikely to be successful. The quality of evidence is low and further research is also needed on potential side effects of eradication therapies and, particularly, the emergence of resistance or new infections.

Question 4: *Should long-term anti-inflammatory agents be used in adult patients with bronchiectasis?*

Recommendation:

- We suggest not offering treatment with inhaled corticosteroids to adults with bronchiectasis (*conditional recommendation, low quality of evidence*).
- We recommend not offering statins for the treatment of bronchiectasis (*strong recommendation, low quality of evidence*).
- We suggest that the diagnosis of bronchiectasis should not affect the use of inhaled corticosteroids in patients with comorbid asthma or COPD (*Best practice advice, indirect evidence*).

We considered only studies of anti-inflammatory drugs that were at least 3 months in duration. Although macrolides may have anti-inflammatory activity their role in bronchiectasis is discussed within PICO question 5 of these guidelines (regarding antibiotics). We identified six systematic reviews[61-66] and 3 studies that met our inclusion criteria [67-69].

Hernando *et al.* reported a double-blind RCT over 6 months with 77 patients allocated to inhaled budesonide 400mcg BD or placebo with a primary outcome of lung function[69]. Tsang *et al.* reported a trial of inhaled fluticasone vs. placebo over 12 months in 86 patients with co-primary endpoints of 24hour sputum volume and annual exacerbation frequency[67]. Mandal *et al.* studied atorvastatin in 30 patients over 6 months compared to a matched group receiving placebo with a primary outcome improvement in cough related quality of life measured by the Leicester cough questionnaire[68]. Overall the three studies included only 193 patients. Two of the studies assessed the effects of anti-inflammatories on exacerbations with a wide confidence interval RR 0.99 (0.76-1.30)[67, 69]. Hence no clear benefit on reducing exacerbations was noted.

The effect on quality of life, using the SGRQ, was only reported in 2 studies (123 patients) [68, 69], with an observed improvement of 0.91 points (below the minimal clinically significant difference of 4 points, CI: -4.51 to +6.33). All 3 studies reported FEV_1 and FVC as lung function outcomes [67-69]. No significant benefit was seen with any of the treatments studied for lung function.

The study design and small number of patients make these studies not optimal for safety assessment. Across the 3 studies the pooled estimate of suffering any adverse event was RR 2.75 (95%CI 1.21-6.25) as compared to control. The adverse effect profile of both inhaled corticosteroids and statins has been well described.

The increase in pooled adverse events were largely driven by Mandal *et al.* who reported that adverse events led to withdrawal from the atorvastatin group (1 case of headache, 1 of diarrhoea, and 2 of combined diarrhoea and headache)[68]. One was withdrawn due to liver function abnormalities at 3 months. Ten (33%) patients receiving atorvastatin had an adverse event versus three (10%) allocated placebo (difference 23%, 95% CI 3–43; p=0.02).

For the inhaled corticosteroid trials in bronchiectasis, adverse event reporting was incomplete. Known and frequent local adverse events across all diseases include dysphonia and oropharyngeal candidiasis. More severe adverse events include: alteration of the hypothalamic-pituitary-adrenal axis function, pneumonia, increased intraocular pressure, formation of cataracts and decreased bone density.

Justification of recommendations

There are no large trials of anti-inflammatory therapies in bronchiectasis and the existing studies show minimal and, in most cases, no clinically significant benefits. The increased frequency of adverse events, particularly with statins, justifies a recommendation against their use. The guideline panel concludes that inhaled corticosteroids do not have a role in the routine management of bronchiectasis. Inhaled corticosteroids have an established role in the treatment of asthma and a proportion of patients with COPD. In the absence of specific data in adult patients with bronchiectasis and these two conditions, the guideline panel concludes that the presence of bronchiectasis alone should not lead to a decision to withdraw inhaled corticosteroids from patients with established asthma or COPD.

Implementation considerations

We recommend randomized controlled trials of inhaled corticosteroids in bronchiectasis who are naïve to inhaled corticosteroid therapy. Inhaled corticosteroid use is, however, already widely used in bronchiectasis. In those already treated with inhaled corticosteroids and no clear history of asthma or COPD a randomized controlled trial of inhaled corticosteroid withdrawal may help define true utility of this widely prescribed therapy.

Question 5: Is long-term antibiotic treatment (≥ 3 months) compared to no treatment beneficial for treating adult bronchiectasis patients?

Recommendations:

- We suggest offering long-term antibiotic treatment for adults with bronchiectasis who have three or more exacerbations per year (*conditional recommendation, moderate quality evidence*). All subsequent recommendations refer to patients with three or more exacerbations per year.

  - We suggest long-term treatment with an inhaled antibiotic for adults with bronchiectasis and chronic *P. aeruginosa* infection (*conditional recommendation, moderate quality evidence*).

  - We suggest long-term treatment with macrolides (azithromycin, erythromycin) for adults with bronchiectasis and chronic *P. aeruginosa* infection in whom an inhaled antibiotic is contraindicated, not tolerated or not feasible (*conditional recommendation, low quality evidence*).

  - We suggest long-term treatment with macrolides (azithromycin, erythromycin) in addition to or in place of an inhaled antibiotic, for adults with bronchiectasis and chronic *P. aeruginosa* infection who have a high exacerbation frequency despite taking an inhaled antibiotic (*conditional recommendation, low quality evidence*).

  - We suggest long-term treatment with macrolides (azithromycin, erythromycin) for adults with bronchiectasis not infected with *P. aeruginosa* (*conditional recommendation, moderate quality evidence*).

  - We suggest long-term treatment with an oral antibiotic (choice based on antibiotic susceptibility and patient tolerance) for adults with bronchiectasis not infected with *P. aeruginosa* in whom macrolides are contraindicated, not tolerated or ineffective (*conditional recommendation, low quality evidence*).

  - We suggest long-term treatment with an inhaled antibiotic for adults with bronchiectasis not infected with *P. aeruginosa* in whom oral antibiotic prophylaxis is contraindicated, not tolerated or ineffective (*conditional recommendation, low quality of evidence*).

We identified 8 systematic reviews[70-77] and 17 relevant studies for this clinical question [37, 57, 78-89][90, 91]. Our evidence summary suggests that long-term antibiotic use, pooling both inhaled and oral antibiotic data, reduces the number of exacerbations, time to first exacerbation, sputum purulence and breathlessness in adults with bronchiectasis; however, they are also associated to more adverse events and bacterial resistance.

Three RCTs evaluating the effect of nebulised antibiotics in adults with bronchiectasis suggested beneficial effects on exacerbation frequency and/or time to first exacerbation [70, 81, 83, 88]. In a study involving 144 adults with bronchiectasis and *P. aeruginosa* infection, colistin 1MU delivered twice daily through the I-neb was not associated with a statistically significant improvement in time to first exacerbation compared to placebo[88]. However, in a pre-planned analysis in adherent individuals (defined as taking ≥81% of doses recorded by the I-neb), the median (25th quartile) time to exacerbation was 168 (65) days versus 103 (37) days in the colistin and placebo groups, respectively (p=0.038). A similar treatment effect was reported in a study evaluating nebulised liposomal ciprofloxacin in 42 adult patients with bronchiectasis and *P. aeruginosa* infection [83]. A 12-month single blind study of nebulised gentamicin in 65 adults with bronchiectasis predominantly infected with *H. influenzae* (n=26, 46%) or *P. aeruginosa* (n=24, 42%) showed significant benefits including fewer exacerbations compared to 0.9% saline-treated patients[81].

Three RCTs showed beneficial effects of macrolide antibiotics (azithromycin or erythromycin) on exacerbation frequency in adults with bronchiectasis: EMBRACE (141 patients on azithromycin or placebo for 6 months)[82], BAT (83 patients on azithromycin or placebo for 12 months)[85] and BLESS (117 patients on erythromycin or placebo for 12 months)[84]. The EMBRACE study showed the rate of event-based exacerbations was 0.59 per patient in the azithromycin group and 1.57 per patient in the placebo group in the 6-month treatment period (rate ratio 0.38, 95% CI 0.26–0.54; p<0.0001); the BAT study showed the median number of exacerbations in the azithromycin group was 0 (IQR 0-1), compared with 2 (IQR 1-3) in the placebo group (p<0.001); and the BLESS study showed erythromycin significantly reduced protocol defined exacerbations compared to placebo (mean, 1.29 [95% CI, 0.93-1.65] vs. 1.97 [95% CI, 1.45-2.48] per patient per year). Doses used in clinical trials or in clinical practice range from 250mg azithromycin daily, 500mg or 250mg three times per week, and erythromycin 400mg twice daily.

Historical RCTs evaluating penicillin and tetracycline based antibiotic regimens also suggest some benefit in adults with bronchiectasis, with two long-term studies reporting less days off work and reduced sputum purulence with oxytetracycline [89] or amoxicillin treatment[78].

Important adverse events were reported with long-term antibiotic treatment. *Diarrhoea* was more

common with oral antibiotics than placebo in the macrolide studies, although treatment discontinuation was rare[71-75]. There was also a 28% increase in the proportion of macrolide-*resistant* commensal oropharyngeal *Streptococci* after 12 months treatment with erythromycin and a macrolide resistance rate of 88% following 12 months of azithromycin [84, 85]. In contrast, there was no antimicrobial resistance reported after 6–12 months of nebulised colistin, dual release liposomal ciprofloxacin or gentamicin[81, 83, 88]. While these specific nebulised preparations were well tolerated, two phase III trials reported more frequent treatment-related adverse events (1.4 and 1.8 times greater) and discontinuations (2.1 and 6.7 times greater) associated with nebulised aztreonam compared to placebo[37]. The most commonly reported adverse events were breathlessness, cough and increased sputum production. The incidence of potential treatment-related adverse events such as QTc prolongation with macrolides, tinnitus/hearing loss with macrolides and inhaled aminoglycosides, and renal dysfunction with inhaled aminoglycosides is not known in people with bronchiectasis, but should be considered when weighing up the potential benefits and harms of long-term antibiotic treatment.

Justification of recommendations (Fig. 4)

The overall balance of desirable effects (particularly fewer exacerbations), undesirable effects (particularly gastrointestinal upset and antimicrobial resistance) and patient values favours long-term antibiotic treatment in selected patients. For individuals with *P. aeruginosa*, the currently available evidence supports continuous use of nebulised colistin[88]or gentamicin[81]). Nebulised aztreonam is not recommended due to the lack of efficacy with regard to quality of life improvement over 2 treatment cycles and a high adverse event rate reported in the pivotal phase III trials[37].Due to the relatively low number of participants with *P. aeruginosa* in the macrolide studies, the use of macrolide antibiotics is suggested as a second-line option in patients with this organism[82, 84, 85]. However, for individuals with no evidence of *P. aeruginosa* infection, macrolide treatment is suggested as first-line treatment due to the high-quality evidence for exacerbation reduction and acceptable side-effect profile[82, 84, 85].

Although the macrolide studies included a minimum exacerbation frequency of 1[82], 2[84] or 3[85] exacerbations in the year preceding enrolment as an entry criterion, the mean exacerbation frequency in the year prior to enrolment in each of the three studies was ≥3. Due to potential undesirable effects, the suggested threshold for starting long-term antibiotic treatment is ≥3 exacerbations per year. However, this threshold should reduce for individuals with: a history of severe exacerbation, relevant comorbidities such as primary/secondary immunodeficiency, patients in whom exacerbations are having a significant impact on their quality of life or those with more severe bronchiectasis[9].

Before considering the prescription of long-term antibiotics, general aspects of bronchiectasis management need to be optimised such as airway clearance and treating modifiable underlying causes. Careful

characterization of sputum pathogens (bacteria, mycobacteria and fungi) before and after implementation of long-term antibiotics is essential to direct antibiotic choices, monitor resistance patterns and identify treatment emergent organisms. Drug toxicity monitoring is also required, most notably with macrolides and inhaled aminoglycosides.

Implementation considerations

The use of inhaled antibiotics is associated with a 10-32% risk of bronchospasm[81, 92] and a supervised test dose with pre- and post- spirometry is recommended. Prior inhalation of a short-acting bronchodilator may prevent bronchospasm and, therefore, is advisable.

Prior to long-term treatment with macrolides, we recommend excluding active NTM infection because macrolide monotherapy can increase the risk of macrolide resistance in NTM.

No cost-effectiveness studies were identified regarding the use of long-term antibiotics in adult patients with bronchiectasis and further research will be required to determine if cyclical or continuous treatment (possibly involving combinations of preparations) is optimal in terms of exacerbation frequency, treatment burden and risk of antimicrobial resistance.

Figure 4 summarises the approach to long-term antibiotic treatment in adults with bronchiectasis summarising the above guideline recommendations.

Question 6: Is long-term mucoactive treatment (≥ 3 months) compared to no treatment beneficial for treating adult bronchiectasis patients?

Recommendation

We suggest offering long-term mucoactive treatment (≥ 3 months) in adult patients with bronchiectasis who have difficulty in expectorating sputum and poor quality of life and where standard airway clearance techniques have failed to control symptoms (*weak recommendation, low quality evidence*).

We recommend not to offer recombinant human DNase to adult patients with bronchiectasis (*strong recommendation, moderate quality evidence*)

Summary of the evidence

Airway clearance adjuncts such as mucolytics and hyperosmolar agents alter mucus viscosity and/or enhance mucociliary clearance. We identified 3 systematic reviews[93-95] and 5 relevant studies meeting inclusion criteria for this clinical question[36, 96-99].Of these five RCTs, two were performed with dry powder mannitol at doses of 320mg (n= 343)[98] and 400mg twice daily (n= 461)[99], one with nebulised recombinant human DNase at a dose of 2.5mg twice daily (n= 349)[36], and two with nebulised hypertonic saline (one with 4mL 7% once daily[96] or 5mL 6% twice daily[97], n=28 and n=40 respectively). Only in two studies [98][36] was the treatment compared to placebo. In one study with mannitol[99] and in both studies with hypertonic saline[96, 97], the treatment was compared to low dose mannitol (50mg twice daily)[99] and isotonic saline [96], respectively. Three previous meta-analyses of mucoactive and inhaled hyperosmolar agents in bronchiectasis prior to the most recent mannitol study[98] found insufficient evidence to draw firm conclusions on the effect of inhaled mucoactive and hyperosmolar treatment due to the significant differences in methodology, patient groups and findings amongst the limited data available[93-95].

Patients with ≥2 exacerbations in the previous year and a baseline minimum SGRQ score of 30 who received mannitol showed a significantly greater improvement in total SGRQ score compared to controls (low dose mannitol), although the difference between arms did not reach the minimal clinically important difference for the total SGRQ score[98]. An improvement in SGRQ components was shown in patients without chronic *P. aeruginosa* infection and with no long-term antibiotic treatment who received hypertonic saline 7%[97].

None of the mucoactive agents significantly reduced the number of exacerbations, and the exacerbation rate was higher in the rhDNase group compared with placebo[36]. In patients with ≥2 exacerbations in the previous year, mannitol increased the time to first exacerbation[99]. In one study with hypertonic saline 7% there were reductions in health care utilisation when comparing prospectively collected data between hypertonic saline and isotonic saline phases[97].

In four studies, a tolerance test was performed at first administration: patients with mannitol-induced bronchospasm (16%) [98, 99] or a decrease in FEV1 of more than 10%[97] or 15%[96] after inhalation of hypertonic saline (7% and 6%, respectively) were excluded.

In the 3-month study, 1.8% of patients randomised to mannitol experienced bronchospasm and 1.3% reported dyspnoea as opposed to none in the placebo group[98]. In the 13-month study, 20.2% of patients in the mannitol arm and 16.7% in the control group experienced adverse events related to study medication, most of which were judged to be mild or moderate[99]. Hypertonic saline was well tolerated with the number of patients with adverse events similar to those of the control groups.

The mannitol studies both showed a significantly increased 24h sputum weight after treatment compared to the control arms, consistent with improved mucociliary clearance [98, 99]. Mean 24h sputum weight decreased progressively during the study in both mannitol and control arms of both studies, but remained higher in the mannitol arms throughout.

No change in lung function was observed in the studies with mannitol [98, 99] or hypertonic saline 6% [96]. However, a significant improvement in FEV1% and FVC% was shown with hypertonic saline 7% at 3 months [97]. In contrast, a decrease in FEV1 was demonstrated in patients treated with RhDNase.

There is insufficient evidence to permit evaluation of the use of oral mucolytics such as carbocisteine for bronchiectasis[94].

Justification of the recommendation

In summary, despite the wide heterogeneity in studies (agent used, study design and treatment duration), overall the literature showed a small improvement in the time to first exacerbation with a slightly elevated but acceptable adverse event profile with inhaled long-term mucoactive agents. The reported improvements in quality of life indicate that a proportion of patients will experience a significant benefit with these agents, but many patients will not.

The current research evidence and the ELF/EMBARC bronchiectasis patient advisory group suggest that patients give intermediate value to this treatment and acknowledge difficulties with its administration. Mucoactive agents are time-consuming and the therapeutic equipment, in the case of nebulizers, may be difficult to take outside of the patient's home.

Implementation considerations

The indication and type of treatment given should be tailored to each individual patient according to their baseline symptom profile (frequency and severity of exacerbations, quality of life, bronchial hyperreactivity, and sputum viscosity), baseline lung function and patient preferences. We suggest testing tolerance prior to starting therapy and to consider β-agonist premedication.

Larger studies should be considered in the future to investigate optimal treatment, dosages, durations and combinations.

QUESTION 7: Is long-term bronchodilator treatment (>=3 months) compared to no treatment beneficial for adult bronchiectasis patients?

Recommendations.

We suggest not routinely offering long-acting bronchodilators for adult patients with bronchiectasis (*conditional recommendation, very low quality of evidence*)

We suggest to offer long acting bronchodilators for patients with significant breathlessness on an individual basis (*weak recommendation, very low quality of evidence*).

We suggest using bronchodilators before physiotherapy, including inhaled mucoactive drugs, as well as before inhaled antibiotics, in order to increase tolerability and optimize pulmonary deposition in diseased areas of the lungs (*good practice point, indirect evidence*).]

We suggest that the diagnosis of bronchiectasis should not affect the use of long acting bronchodilators in patients with comorbid asthma or COPD [44, 45] (*good practice point, indirect evidence*).

Where multiple inhaled therapies are used in the same patient, the sequence of treatments shown in figure 5 is commonly used by members of the task force.

Summary of the evidence

Very limited and indirect evidence is available for the benefit of the long-term treatment with bronchodilators from a systematic review that included a single trial, comparing high-dose inhaled corticosteroids to medium-dose inhaled corticosteroid/Long acting beta agonist combination[100]. The results from this study indicate some positive effects on symptom control / symptomatic improvement, in particular decreased dyspnoea, better cough control, better HRQL (measured by SGRQ symptoms domain), and reduced use of β2-agonist rescue medication. Specific side effects were generally mild (tremor, nervousness and tachycardia). A systematic review identified major methodological and reporting concerns relating to this trial[61]. However, extrapolating evidence from populations with other obstructive airway diseases some bronchiectasis subpopulations may benefit from bronchodilators, in particular subjects with chronic obstructive airflow limitation (FEV1/FVC <0.7; with or without FEV1 reversibility to bronchodilators), or associated asthma in combination with inhaled corticosteroids[44, 45].

Justification of the recommendations

We suggest the use of bronchodilators in patient with significant breathlessness due to the feasibility of application, the easy availability at a primary care level, the comparatively low treatment costs, and

a putatively positive ratio of benefits to adverse events. Appropriate inhalation device selection and inhaler technique training are recommended. If treatment with bronchodilators does not result in a reduction in symptoms it should be discontinued. There is no evidence to support the use of bronchodilators routinely as part of the management of bronchiectasis patients without symptomatic breathlessness. According to both research evidence and patient advisory group feedback, it seems that patients regard this as a low risk and low burden intervention.

Implementation considerations

The intervention is easy to administer and acceptable to the majority of patients. Further investigator-driven research on the benefit of bronchodilators in bronchiectasis in various clinical situations is needed.

QUESTION 8: Are surgical interventions more beneficial compared to standard (non-surgical) treatment for adult BE patients?

Recommendation.

We suggest not offering surgical treatments for adult patients with bronchiectasis with the exception of patients with localised disease and a high exacerbation frequency despite optimisation of all other aspects of their bronchiectasis management (*weak recommendation, very low quality of evidence*).

Summary of the evidence

The rationale for surgical treatment of bronchiectasis is to break the vicious circle of bronchiectasis by removing the lung segments that are no longer functional, and preventing the contamination of adjacent lung zones. The most frequent indication for the operation is recurrent infections with chronic symptoms such as productive cough, purulent sputum and haemoptysis[101, 102].

Lobectomy is the most frequently performed operation, but numerous options have been described (e.g. segmentectomy and pneumonectomy)[103-105]. Surgery is the procedure of choice for massive haemoptysis refractory to bronchial artery embolization, but emergency surgery in unstable patients is associated with higher morbidity and mortality reaching 37%[106]. Although bilateral bronchiectasis (reported in 5.8 to 30% of surgical series) are not an absolute contraindication for surgery[107], other options such as prolonged conservative treatment or bronchial arteries embolization are frequently used as an alternative. The video-assisted thoracoscopic surgery (VATS) is often preferred to better preserve lung function or reduce scarring. In comparison with open surgery, VATS has been reported to produce comparable symptomatic improvement (94 vs. 88%), but with shorter hospital stay, less complications (17.5 vs. 23.7%) and pain after VATS procedures[108]. Contraindications to VATS include major parenchymal or pleural fibrosis, and calcified nodes close to the hilar vessels.

No RCTs of surgical treatment versus standard care were identified. A meta-analysis included 38 observational studies with 5541 patients, dealing with efficiency and safety of different surgical interventions to adult patients with bronchiectasis focused on three main outcomes: mortality, morbidity (adverse events) and quality of life improvement (symptomatic changes defined as reduction or alleviation of preoperative symptoms)[101].

The pooled mortality from 29 studies that focused on adult patients was 1.4% (95% CI, 0.8% - 2.5%)[101]. Post-operative pooled morbidity for adults was analysed in 26 observational studies and was 16.2% (95% CI, 12.5% - 19.8%)[101]. It needs to be emphasized that there are no data comparing morbidity to continued medical non-surgical management alone. Moreover, according to the aforemen-

tioned studies, some of the morbidity is considered relatively minor (air leak, atelectasis, wound infection). Symptomatic changes were analysed in 26 observational studies. In the pooled meta-analysis, complete alleviation of symptoms was seen in 71.5% (95% CI, 68 - 74.9) and reduction of preoperative symptoms was seen in 20.2% of the adult population (95% CI, 17.3 – 23.1)[101]. Other research has shown that extent of residual bronchiectasis and *P. aeruginosa* infection were reported as unfavourable prognostic factors[102].

Justification of the recommendations

Overall, surgical interventions seem to be beneficial only in very carefully selected patients requiring the best risk-benefit profile of improved symptoms against the morbidity associated with surgery. Feedback from the ELF/EMBARC patient advisory group suggests that patients would choose surgery only if there was no effective medical option for treatment and this feedback informs the recommendation.

Implementation considerations

Involvement of an experienced surgeon in partnership with an expert respiratory physician is advisable if surgical treatment is being considered. Attention should be paid to pre-operative nutritional status and pulmonary rehabilitation. More research is needed on surgical interventions. Although a randomized trial would be very challenging future studies should include a matched control population with meticulous description of other treatments used in both populations.

Question 9: Is regular physiotherapy (airway clearance and/or pulmonary rehabilitation) more beneficial than control (no physiotherapy treatment) in adult bronchiectasis patients?

Recommendations.

- We suggest that patients with chronic productive cough or difficulty to expectorate sputum should be taught an airways clearance technique (ACT) by a trained respiratory physiotherapist to perform once or twice daily (*weak recommendation, low quality of evidence*).
- We recommend that adult patients with bronchiectasis and impaired exercise capacity should participate in a pulmonary rehabilitation program and take regular exercise. All interventions should be tailored to the patient's symptoms, physical capability and disease characteristics (*strong recommendation*, *high quality of evidence).*

Summary of the evidence (Figure 6)

In bronchiectasis, it is common belief that physiotherapy can improve mucus clearance and reduce lung inflammation and risk of infection. In addition, it is well accepted by patients. Respiratory physiotherapy includes ACTs and pulmonary rehabilitation (PR)[109, 110]. ACTs consist of breathing techniques e.g. active cycle of breathing and autogenic drainage, sometimes combined with an instrument e.g. flutter or Acapella, that modify expiratory flow and volumes or produce chest wall oscillations in order to increase mucus clearance[111-115]. The principal effect obtained by ACTs is an increase in sputum volume[111, 115, 116] and a reduced impact of cough on quality of life[112-117]. Interesting, but still preliminary data, shows reduced peripheral airways obstruction, less inflammatory cells in sputum and improved exercise capacity after ACTs[112, 115, 117]. The aim of a PR programme is to improve exercise tolerance and quality of life through a tailored standardized exercise protocol[118-120].

We identified 3 systematic reviews[109, 121, 122] and several additional trials. We included a total of 14 clinical trials in our analysis[96, 111, 113-115, 117-120, 123-127].
The pooled analysis shows that PR has a clear impact on exercise capacity immediately after the program and some non-significant trend to improved quality of life (SGRQ)[119, 120, 122, 125, 126]. However, the unpooled study of Mandal *et al*. (PR duration [8 weeks] shorter than for pooled studies) described that improvements on exercise capacity and patient's quality of life may be maintained for a longer period of time[128]. Finally, there is one publication showing an impact of PR (8 weeks of supervised exercise training and review of ACTs) decreasing the frequency of exacerbations (median 1[IQR 1-3]) vs. 2[1-3]; p = 0.012) over 12-month follow-up and longer time to first exacerbation (8 vs. 6

months; p = 0.047)[119]. The reported impact of both ACTs and PR on pulmonary function is not clinically important[110-112, 115, 124]

Justification of the recommendations

The evidence for airways clearance techniques is weak because the studies are small and poorly comparable due to methodological issues. However, most studies demonstrated a significant increase of sputum volume. The evidence is stronger for PR showing improvements in exercise capacity, cough symptoms and quality of life, and possibly a reduction in exacerbations. The benefits of PR are achieved in 6 to 8 weeks and maintained for between 3 to 6 months. Finally, there are no relevant adverse effects and the bronchiectasis patients advisory group value the intervention.

Implementation considerations

The research priorities in physiotherapy are: larger controlled studies with clinical outcomes (exacerbations, cough and quality of life); larger controlled studies including physiotherapy training plus mucoactive agents such as hypertonic saline; the role of PR on exacerbations; and finally, the compliance with these interventions over a longer period of time (>12 months)[129].

SUMMARY

Management of bronchiectasis aims to reduce exacerbations, reduce symptoms, improve quality of life [130][131] and reduce the risk of future complications such as lung function decline[132] and severe exacerbations[133]. Treatment decisions must balance the potential beneficial effects of the intervention against the burden of treatment and the risk of adverse events. It is important to take into account the patients values and preferences in all treatment decisions, alongside the history of exacerbations, quality of life [130][131], severity of disease[9] and underlying aetiology [22], all of which can impact on the patients long-term outcome [134-136].

The purpose of clinical guidelines is to improve the quality of patient care and to promote safe, effective and cost-effective treatment. The majority of recommendations in this guideline are conditional and based on low quality evidence. One outcome of this guideline should be to promote further research into the optimal treatment of patients with bronchiectasis. Bronchiectasis is a rapidly evolving field and our recommendations will require to be revised as additional data becomes available in the coming years.

Acknowledgements

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