Research priorities in bronchiectasis

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Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration

ONLINE SUPPLEMENT

METHODS

Ethical approval was waived for the active involvement of patients as either advisors or participants in questionnaires. In considering patients as advisors, the European Lung Foundation (ELF) adheres to the same guiding principles as the UK's NHS patient and public involvement body INVOLVE (http://www.invo.org.uk/wp-content/uploads/2011/12/INVOLVENRESfinalStatement310309.pdf). According to these principles, the active involvement of patients does not generally raise any ethical concerns for the people who are actively involved because they are not acting in the same way as research participants. They are acting as specialist advisers, providing valuable knowledge and expertise based on their experience of a health condition. Therefore ethical approval is not needed for the active involvement element of the research, where people are involved in planning or

advising on research e.g. helping to develop a protocol, questionnaire or information sheet, member of advisory group, or co-applicant. Furthermore, the patients involved as advisors in the present project were not involved in carrying out research that involves direct contact with study participants e.g. helping to analyse survey data, or communicate directly with survey respondents.

In considering patients as study participants, ethics committee approval is not generally required for online questionnaires as the methodology is considered to pose a minimal risk to the participant. However, ELF adheres to strict ethical principles in questionnaire design, data collection and analysis: transparency of purpose and inclusion/exclusion criteria is always provided at the start of the questionnaire, with a contact name and email address for an ELF staff member provided, so that questions can be asked or any concerns raised. Respondents were free to skip questions and leave the questionnaire/project at any time. The questionnaires were anonymous, as respondents chose to provide a contact email address, e.g. when asked at the end of the questionnaire if they 'would like to receive updates on the project or get involved and represent others with bronchiectasis.' All questionnaire data are stored and password protected on the ELF server, and only accessible by ELF staff members.

FIGURES

Figure A: Questionnaire respondents by country.

Footnotes: n= percentage of respondents.

Figure B: Questionnaire respondent status (patient, parent, relative, carer, or friend of someone with bronchiectasis).

Footnotes: n= percentage of respondents.

Figure C: Questionnaire respondents by age.

Footnotes: n= percentage of respondents.

Figure D: Research topics (in order of importance) to improve how bronchiectasis is managed by doctors.

Footnotes: n= percentage of respondents. NCFBE: non cystic fibrosis bronchiectasis

Figure E: Research topics (in order of importance) to improve how bronchiectasis is treated.

Footnotes: n= percentage of respondents. NCFBE: non-cystic fibrosis bronchiectasis

Figure F: Research topics (in order of importance) to improve how each person's bronchiectasis is monitored.

Footnotes: n= percentage of respondents. CT: computed tomography; NCFBE: non-cystic fibrosis bronchiectasis

Figure G: Research topics (in order of importance) to improve self-management throughout life.

Footnotes: n= percentage of respondents. HCP: health-care professionals.

FULL DISCUSSION OF RESEARCH PRIORITIES

Research priorities commonly identified by both experts and patients

1. What are the causes of bronchiectasis? (Patients) / What are the baseline investigations to evaluate etiologies in patients with bronchiectasis? (Experts)

One of the cornerstones in the management of bronchiectasis is the identification and treatment of underlying causes. Several predisposing factors might be identified including previous severe respiratory infections, allergic bronchopulmonary aspergillosis, impairment of ciliary clearance, primary or secondary immunodeficiency, and other diseases associated to bronchiectasis, such COPD and severe asthma. Despite following guidelines recommendations,

an etiology of bronchiectasis cannot be reached in 40% of the patients, whilst an etiology of bronchiectasis leading to a change in patient's management may be identified in only 13% of the cases [1]. Three of the top five ranked priorities in the questionnaire called for research into the causes and development of bronchiectasis: how bronchiectasis develops and continues; what makes some patients' deteriorate and the causes of bronchiectasis. Many open responses also related to this topic, particularly in the calls for research into genetic factors in the development of the condition, and ultimate hope for a cure [2,3]. The respondents strongly support both research on the causes of the condition, and to slow and prevent the development of bronchiectasis and its symptoms [4]. Further research should integrate basic research from the "-omics" perspective with clinical data in order to identify the possible etiologies among the large group of patients with idiopathic bronchiectasis. An early example of this was recently published by Szymanski et al. who used exome sequencing to identify multigenic susceptibility factors for bronchiectasis associated with NTM disease [5].

Consensus statements: 1) DNA biobanks linked to well phenotyped patient cohorts should be established to enable underlying genetic susceptibility to bronchiectasis to be established; 2) Observational research in large patient cohorts is needed to establish the natural history of bronchiectasis due to different aetiologies.

2. What are the triggers of an exacerbation? (Patients) / What are the causes of an exacerbation of bronchiectasis? (Experts)

Exacerbations of bronchiectasis are characterized by increases in cough frequency, sputum volume and purulence and represent a significant cause of morbidity in bronchiectasis [6,7]. Pulmonary exacerbations are associated with disease progression and frequent or severe exacerbations are an independent risk factor for mortality. The respondents strongly support research into the triggers of exacerbation and expanded on this priority by calling for research to focus on the need to reduce the frequency, duration and severity of exacerbations.

Although in asthma and COPD the presence and prevalence of non-infectious triggers of exacerbations have been recognized during the past decade, these data are still missing in bronchiectasis [8]. The "vicious-cycle" hypothesis that characterized the physiopathology of bronchiectasis patients in stable state does not rule out the possibility that non-infectious triggers, including indoor and outdoor air pollution, might cause exacerbations and further prospective observational studies are needed in this area [9].

From an infective point of view, changes in airway bacterial community composition, emergence of new strains, as well as spread of infection by the same species to new regions of the lung might trigger exacerbations [10-12]. The most common organisms seen during an exacerbation are *P. aeruginosa*, *H. influenzae, S. pneumoniae*, *S. aureus* and *M. catarrhalis* [13, 14]. The need of moving beyond conventional microbiological techniques has been suggested by the following observations: a) total bacterial density seems not to increase significantly at the onset of exacerbation in comparison to stable state; b) patients might show a good clinical response when an antibiotic not targeted on the colonizing pathogen has used and that pathogens are frequently isolated in stable patients [15]. New airway infection caused by organisms present in low abundance (and thus that may be not detected with conventional

techniques) yet identifiable by metagenomic approaches could help us understand what is responsible for triggering a new exacerbation [15]. However, it could be also possible that exacerbations may also be driven by changes and/or adaptation in strains that cannot be detected by such approaches and hence a metabolomics approach may help.

Finally, the role of viruses in triggering infective exacerbations should also be better defined. Coronavirus, rhinovirus and influenza A/B seem to be the most common viruses identified during an exacerbation and virus-positive exacerbations are associated with high levels of systemic and airway inflammation [16]. The interaction between respiratory viruses and bacteria in stable and acute exacerbation of bronchiectasis should be also investigated in light of previous evidence suggesting that respiratory viruses may precipitate secondary bacterial infection in COPD and CF [17, 18].

Consensus statement: A comprehensive study enrolling patients when stable and during exacerbation should be conducted, evaluating the impact of bacteria, viruses, fungi and non-infectious stimuli to identify the cause(s) of bronchiectasis exacerbations.

3. *How can we improve the access to physio and home-use techniques? (Patients) / When should airways drainage techniques be started in patients with bronchiectasis and which one is the most effective and pragmatic? (Experts)*

Impaired mucociliary clearance is one of the key characteristics of bronchiectasis [19]. Interventions aimed at promoting clearance of excess mucus are therefore a mainstay of management. Consensus guideline suggest that all patients with bronchiectasis should receive instructions on performing physiotherapy and healthcare workers should tailor different techniques to patients' preference in order to increase patients' adherence [20]. Few studies have explored the impact of physiotherapy in bronchiectasis. A recent Cochrane review evaluated five trials with a total of 51 participants and indicated that airway clearance techniques are safe and allow a better sputum expectoration with an increase in patients' quality of life [21]. Current guidelines on bronchiectasis also recommend pulmonary rehabilitation, in order to improve exercise tolerance and quality of life. Although evidence on pulmonary rehabilitation is scarce, most of the studies demonstrated an increase in patients' performance and quality of life, and an increase of the time to the next exacerbation [22-24]. A study of 75 patients with bronchiectasis indicated that only 41% of patients were adherent to prescribed chest clearance regimes [25]. Both physicians and patients agreed that additional controlled trials of these interventions would be beneficial but that the priority may be in identifying methods that are accessible and that encourage adherence.

Consensus statement: Studies are required to optimize compliance and access to chest physiotherapy and pulmonary rehabilitation in bronchiectasis.

4. Identify patients at risk of poor outcomes (Patients) / What are the risk factors and causes for fast progression and poor outcomes in patients with bronchiectasis? (Experts)

From both patient and experts' perspective, it is crucial that healthcare workers can identify which patients are at greater risk of poor outcomes and in need of urgent treatment [26]. Recently, two scores have been proposed to predict adverse outcomes in bronchiectasis: the Bronchiectasis Severity Index (BSI) and the FACED score [27]. The BSI has been shown to accurately identify patients at the highest risk of complications, including exacerbations and impaired quality of life, and so far is the only prediction tool for bronchiectasis that has been externally validated in large cohorts. Expert opinion suggests that disease severity may be useful as a framework for clinical decision allowing the appropriate targeting of therapies including long-term macrolides, inhaled antibiotic treatment and airway adjuncts. Clinical prediction tools require to be internationally validated and then to demonstrate improvements in clinical management after implementation into clinical practice.

In case of progressive decline in lung function, respiratory failure and diffuse disease, lung transplantation might be a therapeutic option with suitable long-term survival and an improvement in quality of life in appropriately selected patients [28]. An accurate assessment of prognosis is essential for rational decisions regarding transplantation in bronchiectasis, and scoring may also be helpful in this context [29].

Several other factors need future multicentre, prospective, longitudinal studies to evaluate drivers of faster disease progression including the evaluation of microorganisms other than *P. aeruginosa*, microbiome parameters such as species diversity and richness, local and systemic inflammatory biomarkers and, other measurements of lung function impairment (e.g. lung

clearance index). The importance of comorbidities should also be explored as they may be amenable to treatment [30].

Consensus statements: 1) A deeper understanding of the inflammatory pathways in bronchiectasis is needed to develop new therapies. We recommend using emerging techniques and technologies (particularly proteomics, metabolomics and genomics) in large well-characterized cohorts to identify new treatment targets and deeper patient phenotyping; 2) An implementation study should be performed to demonstrate if the use of bronchiectasis severity scores could improve patient care.

Important research priorities identified by experts

1. When and how should Pseudomonas aeruginosa be eradicated in patients with bronchiectasis and does eradication result in improved outcomes?

Pseudomonas aeruginosa is persistently isolated in up to 35% of patients with bronchiectasis. A recent study found that *P. aeruginosa* colonization is associated with a 3-fold increase risk of death, a nearly 7-fold increase risk of hospital admissions, worse quality of life and more frequent exacerbations [31]. Evidence from CF suggests that attempts at eradication therapy targeting *Pseudomonas* can have success in converting patients to culture negative status [32]. The data both in bronchiectasis and CF are of limited quality in defining both the early

outcomes and long-term benefits. There are no large adequately powered studies to inform current practice, with most studies limited to observational case series [33,34]. Difficulties remain in determining the correct population to study. There is however a perception that patients with new acquisition of *Pseudomonas* may be the most amenable to eradication therapies. Notably, a challenging aspect for future trials designs is the recent observation that according to standard culture definitions *Pseudomonas* may "clear" spontaneously particularly in those with milder disease [35].

Other studies using inhaled antibiotics therapies focused on treating those with persistent infection with the primary aim of reducing exacerbations [36]. An unexpected benefit seen in these trials is that they have consistently demonstrated small but significant rates of "eradication" of up to 10-15% [37,38]. Prior "eradication" therapeutic approaches have included pulmonary-targeted therapies such as nebulized antibiotics. Treatment periods have varied dependent on the phase of development and the intent for exacerbation prevention. In general, new acquisition eradication studies have been shorter in duration such as 3 months whilst those using nebulized therapies were aiming to reduce exacerbations in those persistent infection have been as long as 12 months.

From the available literature there are significant variations in all aspects of study design. Future randomized controlled studies will need clear definitions, techniques used and timing of testing for eradication. Examples of methodological variation may include culture of *Pseudomonas* at 3, 6 or 12 months on spontaneous sputa during treatment. Additional variables may include studying induced sputa (as inhaled antibiotic regimens do reduce sputum

volume), using non-culture based techniques (polymerase chain reaction) for diagnosis of *Pseudomonas* persistence and variation in timing of the sampling.

Consensus statement: A randomized controlled trial of *Pseudomonas aeruginosa* eradication therapy, compared to no eradication treatment, should be performed.

2. What is the optimal antibiotic regimen (dosage, how many antibiotics, type, oral vs. intravenous vs. inhaled/nebulized, length of therapy) for an exacerbation of bronchiectasis?

Most of the bronchiectasis patients experiencing an exacerbation receive antibiotics, and these have been proven to reduce systemic inflammation, sputum inflammatory biomarkers, sputum volume and purulence, and bacterial density [14]. However, data evaluating the use of antibiotics during an exacerbation are extremely heterogeneous in terms of the antimicrobials used, route of administration, duration of treatment and clinical/microbiological endpoints. Last but not least, there are no randomized placebo-controlled trials of antibiotic regimes during exacerbation. This may be important as several classes of antibiotics have interesting additional effects beyond their antimicrobial actions e.g. macrolides have anti-inflammatory activity whilst tetracycline's may inhibit stromal remodelling and tissue damage via their effects on matrix metalloproteinases.

International guidelines suggest that both oral and intravenous antibiotic choices should be guided, where possible, by previous sputum microbiology. However, it should be also underlined that the role of antibiotic sensitivity testing in patients with bronchiectasis and

chronic *P. aeruginosa* infection is contentious due to possible sampling errors (sputum plug from a quiescent area of the lung), hypermutation and the poor correlation between *in vitro* antibiotic sensitivity test results and clinical outcomes [39]. Clinical experience suggests that better outcomes are seen with higher dose oral regimens, which presumably reflects their superiority over conventional doses in achieving adequate antibiotic concentrations within the lumen of bronchiectatic airways. This is particularly relevant in the context of chronic infection where bacteria are often resistant and protected by biofilms. The appropriate length of treatment for exacerbations is also unknown, while consensus guidelines recommend 14 days of treatment with antibiotic therapy. The optimal duration of treatment is importance as prolonged treatment carries a higher risk of driving antibiotic side effects, including resistance. Murray and colleagues prospectively studied the effect of intravenous antibiotic therapy on clinical and laboratory end-points in patients with bronchiectasis exacerbations [14]. They demonstrated significant reductions in 24-hour sputum volume and C-reactive protein, with improvements in quality of life, exercise capacity and clearance of bacteria after 14 days treatment. Finally, the possibility of treating exacerbations of bronchiectasis with nebulized antibiotics has also been tested in the past [40]. Inhaled tobramycin solution was added to oral ciprofloxacin to treat exacerbation in the context of *P. aeruginosa* infection, showing a superior microbiological efficacy compared to ciprofloxacin alone.

Consensus statements: 1) A randomized controlled trial comparing at least 14 days of antibiotic treatment for exacerbations with shorter course treatments is required.

3. What are the prevalence and characteristics of microbiological colonization, in patients with bronchiectasis across Europe (including bacteria, viruses, fungi, non-tuberculous mycobacteria and resistant microorganisms)?

Diverse polymicrobial communities exist within bronchiectasis-affected airways, causing chronic infection or exacerbations. *H. influenzae* and *P. aeruginosa* are the most commonly isolated organisms in several European studies using aerobic selective cultures, although no organisms are isolated in 23-27% of patients [4,15,41-43]. However, new methods to study lung microbiota found that the diversity of airway infection is underestimated. First of all, when strict anaerobic cultures are applied, anaerobic bacteria might be found in up to 83% of sputum samples [44]. Second, using 16S rRNA gene amplicon sequencing, three taxa, *Streptococcaceae*, *Pseudomonadaceae* and *Pasturellaceae* seem to be dominant. Furthermore, a considerably greater bacterial diversity within sputa may be observed in comparison to cultures, with the presence of less abundant and potentially more difficult-to-culture bacterial genera being detected including anaerobic *Prevotellaceae*, *Veillonellaceae* and *Actinomycetaceae* [15,43]. Most microbiome studies in bronchiectasis to date have been small, and therefore the clinical importance of this information is uncertain.

Few data have been published regarding the prevalence of fungal colonization. The prevalence of at least one isolation of *Aspergillus* spp has been found between 2% and 24%, whereas one study found *Candida* in 45% of samples [4,41,44]. The prevalence of isolation of *Aspergillus* spp and *Candida* in more than two sputum samples taken at least 6 months apart was observed in 8.7% and 34%, respectively [44]. It is now possible to perform sequencing of the fungal

"mycobiome" in a similar way to that described above for bacteria, and such studies will help to answer whether fungal colonization has clinical relevance. The prevalence of non-tuberculous mycobacteria (NTM) in Europe is lower than 10%, although there seems to be a broad geographic variation in prevalence [45]. Whilst this may reflect variation in sampling frequency it is highly likely there are environmental factors that play a role in this. The role of NTM between innocent colonizers or those causing chronic infection and the predisposing factors to this needs to be differentiated. Finally, there is a paucity of data regarding the isolation of viruses and multi-resistant bacteria [16]. The prevalence of methicillin-resistant *S. aureus* was 1.3% in the study by Chalmers and co-workers, whereas multiresistant Gram-negative bacteria were 4.5% [35].

Given this knowledge gap in Europe, multicentre studies with a large number of patients are needed to find out the real prevalence of airway pathogens across Europe, as well as data relating to the microorganisms that are implicated and antibiotic sensitivity patterns. Longitudinal studies will be required to study the factors that may have an influence on regional differences and the role of anaerobic bacteria, multi-resistant bacteria, virus, NTM and fungi in chronic infection and exacerbations. Finally, it is also desirable that agreed definitions of important concepts such as initial colonization, intermittent isolation, chronic colonization, chronic infection, eradication, and exacerbation should be adopted across Europe.

Consensus statements: 1) We suggest studies of the microbiome (incorporating bacteria and potentially fungi) in bronchiectasis linked to detailed clinical phenotyping data; 2) A longitudinal study of the bacteriology of bronchiectasis incorporating data on antibiotic resistance is needed.

4. What is the impact of long-term antibiotic therapy on microbial resistances?

The wide use of both systemic and inhaled antibiotics in patients with bronchiectasis causes rising concern about antimicrobial resistance, particularly for *P. aeruginosa* whose rate of resistance to ciprofloxacin could grow along with its spread [46,47]. Factors associated with the risk of antibiotic resistance may be antibiotic-related (type of antibiotic, frequency, doses, duration, local concentration) and pathogen-related (hypermutation, biofilm production) [48-51]. Since few options are currently available to intervene on microbial characteristics, most of the current efforts are dedicated to improve antibiotics characteristics and to optimize their administration. New formulations, such as dry powder or liposomal solution for inhalation, and new molecules are being investigated in order to improve antibiotic tolerance and efficacy [52]. Targeting such drugs to the lung may limit the development of resistance by avoiding affecting the enteric flora. Although recent guidelines recommend higher antibiotic doses and longer duration of therapy to treat exacerbations, it is still debated whether both a dual agent therapy (systemic *plus* inhaled antibiotic) and shorter duration can be preferable not only to improve clinical outcomes and reduce side effects, but also to minimise antimicrobial resistance [40,53-55].

Regarding the use of long-term antibiotics, periodic administration of rotating or fixed antibiotics is potentially associated with increased resistance and side effects, and risk of selection of fungal infection [44,56-58]. Inhaled antibiotics have been traditionally administered

in 28-day cycles because of a theoretical benefit in terms of lower resistance, although data comparing to continuous administration is lacking. Although prolonged therapy with macrolides is effective in reducing exacerbations, there is a clear risk of antibiotic resistance for both sputum and oropharyngeal flora and a more careful selection of patients undergoing this treatment is recommended [59-62]. Long term inhaled therapy offers clear advantages upon systemic antibiotics in both CF and non-CF bronchiectasis in terms of disease control and side effects, although clinical response and tolerability are quite variable [63,64]. The risk of antimicrobial resistance to inhaled antibiotics seems to be very low despite prolonged and continuous administration, perhaps due to the high concentrations achieved in the airways [36]. Nevertheless as the use of inhaled antibiotics increases, and as new inhaled antibiotics as licensed there is a need to carefully monitor antibiotic resistance rates emerging in existing pathogens or the selection of new inherently resistant organisms.

A number of unresolved issues deserve attention for future research, including the possibility to evaluate longitudinal data on the acquisition of resistance for pathogens that chronically infect bronchiectasis patients. Furthermore, an evaluation of risk factors, both host-, antibiotic- and pathogen-related, leading to antibiotic resistance should be adequately conducted.

Consensus statements: 1) Longitudinal studies should be conducted in patients receiving oral and inhaled antibiotics to monitor for the emergence of antibiotic resistance; 2) Studies should ideally evaluate whether cyclical or continuous administration of long-term antibiotics is superior both in terms of clinical efficacy and the emergence of resistance.

5. *When should a long-term suppressive antibiotic therapy (either oral or inhaled/nebulized) be started in patients with bronchiectasis (according to the presence or not of P. aeruginosa or other pathogens) and what should be the endpoints for efficacy?*

Long-term suppressive antibiotic treatment is increasingly used to treat chronic bronchial infection. Several reports describe the chronic use of inhaled antibiotics in about 10% and of macrolides in about 30% of all bronchiectasis patients [65-68]. The use of inhaled antibiotics has been predominantly in patients with *P. aeruginosa* colonization with limited data in patients with other pathogens [69].

Various inhaled antibiotics have been tested to reduce bacterial load from bronchiectasis patients' airways and related symptoms and exacerbations such as tobramycin [70,71], colistin [72], gentamicin [69], and aztreonam [73]. Despite some differences among trials and antibiotics (duration, doses, etc.) inhaled antibiotics have demonstrated to be safe and efficacious in reducing the sputum bacterial density, increase *P. aeruginosa* eradication and attenuate the risk of exacerbation in cystic fibrosis, however, although some risk of wheeze and bronchospasm has to taken into account [64]. In bronchiectasis data are more limited and results have been mixed. Aztreonam failed to demonstrate any improvement in quality of life or exacerbations in two phase 3 trials, while colistin narrowly failed to reach its primary end-point of time to next exacerbation, although achieved a significant improvement in health related quality of life and improved exacerbations in those compliant with therapy. Gentamicin

was evaluated in a small, randomised, single-blinded study of 57 patients compared to 0.9% saline and caused a significant reduction in bacterial load and exacerbations.

Tolerability can be a major issue with inhaled antibiotics in bronchiectasis, with an increase in adverse events in the aztreonam trials, and a number of other trials. As a result of the challenges in these trials, none are as yet licensed for use in bronchiectasis by authorities in Europe or the United States. At the time of writing, large phase 3 trials of two formulations of pulmonary-targeted ciprofloxacin are ongoing.

With regards to oral long-term macrolides, 3 different trials have largely demonstrated their usefulness in reducing the number of exacerbations with consequent improvement of quality of life and in some cases with slower lung function decline [59-61]. Nevertheless, it is important to remember several concerns about long-term use of macrolides: including antimicrobial resistance [61,74]; the potential to promote macrolide-resistant NTM [75-77] and an increased risk of cardiovascular complications has been reported [78,79]. In conclusion, it seems that macrolides are clearly beneficial in patients with bronchiectasis, but the optimal patient population to benefit has not been defined. The inclusion criteria of the trials were broad, including patients with 1 exacerbation [59], 2 exacerbations [61] or 3 exacerbations [60] in the previous year and each trial used a different regimen (azithromycin 500mg three times per week or 250mg daily, or erythromycin ethylsuccinate 400mg bd). Trials had either 6-month [59] or 12-month [60,61] treatment duration and the long-term safety and resistance impact of these drugs is unknown.

Consensus statements: 1) Further studies are required to define the optimal patient population to benefit from long-term macrolide therapy; 2) More “real world” data on the

long-term safety and resistance impact of macrolide treatment are required; 3) Inhaled antibiotics such as colistin and gentamicin should be subject to definitive phase III trials to demonstrate a reduction in exacerbations and improvements in quality of life.

6. What are the key factors leading to P. aeruginosa colonization?

The prognostic implications of *P. aeruginosa* colonization have already been discussed above. This relationship between *P. aeruginosa* and a worse phenotype is likely to be both cause and effect, with *P. aeruginosa* more likely to colonize patients with more severe disease, but studies also demonstrating an independent effect of *P. aeruginosa* on morbidity and mortality. The reason that some patients with bronchiectasis become colonized with *P. aeruginosa* while the majority do not is unexplained. Understanding why this happens is critical, given the clinical implications and the significant hospitalisation and other costs associated with the treatment of *P. aeruginosa* infections.

Genetic studies may identify host risk factors for *P. aeruginosa* colonization, and a modest effect of Mannose binding lectin polymorphisms on susceptibility has been shown in bronchiectasis and in cystic fibrosis [80,81]. In addition to host factors, microbial factors are also important in *P. aeruginosa* colonization. In CF there is clear evidence of person-person transmission and epidemic strains have been well described in the literature leading to strict patient isolation [82]. Similar cross infections have not been demonstrated to date in non-CF bronchiectasis [83]. Different *P. aeruginosa* strains in CF have been recognized to have variation

in *in vitro* phenotypes that appear to translate into clinically meaningful outcomes [84,85]. The concept of an airway polymicrobial community is being increasingly recognized and the interaction between various microbes and its impact on *P. aeruginosa* colonization is likely to provide further insights in the future.

Large, longitudinal, observational studies should help answer many aspects of this research question. In particular, the assessment of a large cohort of patients at first *P. aeruginosa* colonization will help determine the risk factors for its development and a comparison of the clinical course pre and post colonization may help determine the independent impact that *P. aeruginosa*. Future cohort studies assessing the airway microbiome in patients with and without *P. aeruginosa* colonization may also provide clues as to how the complex microbial interactions can affect risk. Finally, multicentre *P. aeruginosa* genotyping and epidemiological studies may help answer the question of cross-infection and provide insights into the genotype-phenotype- clinical outcomes associations with *P. aeruginosa* infection.

Consensus statements: 1) Mechanistic studies investigating the genetic, microbiological, inflammatory and clinical susceptibility factors for *P. aeruginosa* colonization should be conducted; 2) Long-term cohort studies are needed to identify which patients acquire *P. aeruginosa* colonization and to identify its independent effects on outcome.

7. What are the indications of oral versus inhaled/nebulized long-term suppressive antibiotic treatment?

There are no head to head trials of oral versus inhaled antibiotics. The criteria to choose between oral macrolides and inhaled antibiotics are still not clear and the decision is still empirical and based on personal experience and local healthcare prescription rules. Nevertheless it is clear that some factors could justify the antibiotic choice such as the presence of specific antibiotic allergies and side effects, the patients' preferences and ability to manage inhalations, the co-existence of rhinosinusitis (which may also benefit from macrolides) and cardiovascular comorbidities. In the absence of head to head trials, large registries should provide important information about treatment patterns. In addition, ongoing randomized trials of inhaled antibiotics which include macrolide-treated patients will evaluate the important question of whether inhaled antibiotics can provide added benefit.

Consensus statement: Comparative studies are needed to determine the optimal choice between oral and inhaled antibiotic treatment in patients with and without *P. aeruginosa* colonization.

8. What are the best molecule, dose, regimen and duration for long-term oral antibiotic therapy in patients with bronchiectasis (according to the presence or not of Pseudomonas aeruginosa or other pathogens)?

Long-term oral antibiotic therapy has been a key part of clinical management for bronchiectasis for decades, with some limited evidence of efficacy from long-term beta-lactams in the 1980's. Macrolides, however, have been favoured due to *in vitro* evidence that they have anti-inflammatory and immunomodulatory effects in addition to their broad antimicrobial activity

against pathogens found in bronchiectasis [86]. Three major studies recently demonstrated the efficacy of long-term macrolides in bronchiectasis in double-blind randomized trials [59-61].

Key questions remain regarding oral antibiotic therapy including: Do macrolides have to be continued lifelong, or can they be withdrawn e.g. after 12 months? The most appropriate dose and macrolide agent to minimise side effects and development of antimicrobial resistance has not been determined. It is not known if alternative oral antibiotic agents such as tetracyclines or beta-lactams are equally effective when given long-term. As the maximum duration of macrolide treatment was 12 months, it is not known if the effectiveness of macrolides wanes over time as antibiotic resistance develops or if effectiveness is sustained. These questions may be addressed by controlled trials or by multicentre, international registries.

Consensus statement: Randomized controlled trials should address whether alternative long-term oral antibiotics (other than macrolides) are effective at reducing exacerbations.

Important research priorities identified by patients

Other important themes have been identified from the top ranking patient priorities with a special attention focused on condition management, communication and information. These areas were all strongly supported by the expert working group.

1. Condition management

The questionnaire identified a number of research topics that could help improve the management of their bronchiectasis. Over 96% of respondents felt that their bronchiectasis could be better managed through having a self-management plan co-designed with their HCP, and access to physiotherapy/pulmonary rehabilitation, which also includes teaching them how to use techniques/equipment at home [4,23,87,88]. Self-management plans facilitated by good communication between patients and HCPs empower patients to manage and cope with their condition more confidently and independently [89,90]. An important component of these self-management strategies, and in reducing hospitalization, is the awareness of HCPs' of bronchiectasis and available and appropriate community care and physiotherapy services [87,91]. Research into this area would evidence the effectiveness of self-management strategies to support their widespread implementation in bronchiectasis [90].

Consensus statement: Studies should be conducted to determine the effectiveness of patient self-management in bronchiectasis and adherence to treatment.

2. Communication and information

One of the top priorities for patients was good communication between HCPs and each patient. Patients also highly ranked the need for access to reliable plain language information on living with bronchiectasis [89]. This shows that patients' do not feel their information needs are being met, as they are struggling to find accurate information to help them live with their condition, which is a role that can be supported by the clear communication of information to patients by HCPs, both at the point of diagnosis and as their condition/needs change [89]. Increasingly patients look to the internet for information on their condition; therefore healthcare

professionals can provide an invaluable service by signposting patients and their carers/families to reliable plain language information both online and in paper format i.e. medically accurate, plain language information leaflets. This role can be especially important for people with bronchiectasis and other neglected and under-resourced conditions, where there is less public and healthcare professional awareness and few widely available multilingual information leaflets, patient organisations and support groups. The potential for enhanced information packages or patient alert systems to help adherence and self-management offers a potentially cost effective solution acceptable to patients, with examples available in other disease areas and with patients involved in the development of resources.

Consensus statements: 1) Further research with patients as partners could explore the specific information needs of bronchiectasis patients, effective HCP and patient communication strategies, and develop improved patient-reported outcomes; 2) A multidisciplinary education programme is needed for bronchiectasis to increase awareness among non-specialists in secondary care and among primary care.

REFERENCES

1. Lonni S, Chalmers JD, Goeminne PC, McDonnell MJ, Dimakou K, De Soyza A, Polverino E, Van de Kerkhove C, Rutherford R, Davison J, Rosales E, Pesci A, Restrepo MI, Aliberti S. Etiology of Non-Cystic Fibrosis Bronchiectasis in Adults and Its Correlation to Disease Severity. Ann Am Thorac Soc 2015; Oct 2. Epub ahead of print

2. Gould CM, Freeman AF, Olivier KN. Genetic Causes of Bronchiectasis. Clinics in Chest Medicine 2012; 33: 249–263.

3. Organtzis I, Papakosta D, Foyka E, Lampaki S, Lagoudi K, Moumtzi D, Kostanta S, Sourla E, Papadaki E. 035. Bronchiectasis diagnosis and treatment. J Thorac Dis 2015; 7: AB035.

4. Pasteur MC, Helliwell SM, Houghton SJ, Webb SC, Foweraker JE, Coulden RA, Flower CD, Bilton D, Keogan MT. An investigation into causative factors in patients with bronchiectasis. Am J Respir Crit Care Med 2000; 162: 1277-1284.

5. Szymanski EP, Leung JM, Fowler CJ, Haney C, Hsu AP, Chen F, Duggal P, Oler AJ, McCormack R, Podack E, Drummond RA, Lionakis MS, Browne SK, Prevots DR, Knowles M, Cutting G, Liu X, Devine SE, Fraser CM, Tettelin H, Olivier KN, Holland SM. Pulmonary nontuberculous Mycobacterial infection: a multisystem, multigenic disease. Am J Respir Crit Care Med 2015; 192: 618-628.

6. Chang AB, Bilton D. Exacerbations in cystic fibrosis. 4. Non–cystic fibrosis bronchiectasis. Thorax 2008; 63: 269–276.

7. King PT, Holdsworth SR, Freezer NJ, Villanueva E, Holmes PW. Characterisation of the onset and presenting clinical features of adult bronchiectasis. Respir Med 2006; 100: 2183–2189.

8. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, Fabbri LM, Johnston SL. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med 2006; 173: 1114-1121.

9. Goeminne PC, Bijnens E, Nemery B, Nawrot TS, Dupont LJ. Impact of traffic related air pollution indicators on non-cystic fibrosis bronchiectasis mortality: a cohort analysis. Respir Res 2014; 15: 108.

10. Fodor AA, Klem ER, Gilpin DF, Elborn JS, Boucher RC, Tunney MM, Wolfgang MC. The adult cystic fibrosis airway microbiota is stable over time and infection type, and highly resilient to antibiotic treatment of exacerbations. PLoS One 2012; 7: e45001.

11. Han MK, Huang YJ, Lipuma JJ, Boushey HA, Boucher RC, Cookson WO, Curtis JL, Erb-Downward J, Lynch SV, Sethi S, Toews GB, Young VB, Wolfgang MC, Huffnagle GB, Martinez FJ. Significance of the microbiome in obstructive lung disease. Thorax 2012; 67: 456-463.

12. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med 2008; 359: 2355-2365.

13. Finklea JD, Khan G, Thomas S, Song J, Myers D, Arroliga AC. Predictors of mortality in hospitalized patients with acute exacerbation of bronchiectasis. Respir Med 2010; 104: 816-821.

14. Murray MP, Turnbull K, Macquarrie S, Hill AT. Assessing response to treatment of exacerbations of bronchiectasis in adults. Eur Respir J 2009; 33: 312-318.

15. Tunney MM, Einarsson GG, Wei L, Drain M, Klem ER, Cardwell C, Ennis M, Boucher RC, Wolfgang MC, Elborn JS. Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation. Am J Respir Crit Care Med 2013; 187: 1118-1126.

16. Gao Y, Guan W, Xu G, Lin Z, Tang Y, Lin Z, Gao Y, Li H, Zhong N, Zhang G, Chen R. The role of viral infection in pulmonary exacerbations of bronchiectasis in adults: A prospective study. Chest 2015; 147: 1635-1643.

17. Johansen HK, Høiby N. Seasonal onset of initial colonisation and chronic infection with Pseudomonas aeruginosa in patients with cystic fibrosis in Denmark. Thorax 1992; 47: 109-111.

18. Mallia P, Footitt J, Sotero R, Jepson A, Contoli M, Trujillo-Torralbo MB, Kebadze T, Aniscenko J, Oleszkiewicz G, Gray K, Message SD, Ito K, Barnes PJ, Adcock IM, Papi A, Stanciu LA, Elkin SL, Kon OM, Johnson M, Johnston SL. Rhinovirus infection induces degradation of antimicrobial peptides and secondary bacterial infection in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2012; 186: 1117-1124.

19. Currie DC, Pavia D, Agnew JE, Lopez-Vidriero MT, Diamond PD, Cole PJ, Clarke SW. Impaired tracheobronchial clearance in bronchiectasis. Thorax 1987; 42: 126–130.

20. Flude LJ, Agent P, Bilton D. Chest physiotherapy techniques in bronchiectasis. Clin Chest Med 2012; 33: 351–361.

21. Lee AL, Burge A, Holland AE. Airway clearance techniques for bronchiectasis. Cochrane Database Syst Rev 2013; 5: CD008351.

22. Ong HK, Lee AL, Hill CJ, Holland AE, Denehy L. Effects of pulmonary rehabilitation in bronchiectasis: A retrospective study. Chron Respir Dis 2011; 8: 21-30.

23. Mandal P, Sidhu MK, Kope L, Pollock W, Stevenson LM, Pentland JL, Turnbull K, Mac Quarrie S, Hill AT. A pilot study of pulmonary rehabilitation and chest physiotherapy versus chest physiotherapy alone in bronchiectasis. Respir Med 2012; 106: 1647-1654.

24. Lee AL, Hill CJ, Cecins N, Jenkins S, McDonald CF, Burge AT, Rautela L, Stirling RG, Thompson PJ, Holland AE. The short and long term effects of exercise training in non-cystic fibrosis bronchiectasis- a randomised controlled trial. Respir Res 2014; 15: 44.

25. McCullough AR, Tunney MM, Quittner AL, Elborn JS, Bradley JM, Hughes CM. Treatment adherence and health outcomes in patients with bronchiectasis. BMC Pulm Med 2014; 14: 107.

26. Mandala P, Morice AH, Chalmers JD, Hill AT. Symptoms of airway reflux predict exacerbations and quality of life in bronchiectasis. Respiratory Medicine 2013; 107: 1008–1013.

27. Martínez-García MÁ, de Gracia J, Vendrell Relat M, Girón RM, Máiz Carro L, de la Rosa Carrillo D, Olveira C. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. Eur Respir J 2014; 43: 1357-1367.

28. Mauchley DC, Daley CL, Iseman MD, Mitchell JD. Pulmonary resection and lung transplantation for bronchiectasis. Clin Chest Med 2012; 33: 387-396.

29. Hayes D Jr, Kopp BT, Tobias JD, Woodley FW, Mansour HM, Tumin D, Kirkby SE. Survival in Patients with Advanced Non-cystic Fibrosis Bronchiectasis Versus Cystic Fibrosis on the Waitlist for Lung Transplantation. Lung 2015 in press

30. Grillo L, Irving S, Hansell DM, Nair A, Annan B, Ward S, Bilton D, Main E, Davies J, Bush A, Wilson R, Loebinger MR. The reproducibility and responsiveness of the lung clearance index in bronchiectasis. Eur Respir J 2015 Sep 4. Epub ahead of print

31. Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A Comprehensive Analysis of the Impact of Pseudomonas aeruginosa Colonisation on Prognosis in Adult

Bronchiectasis. Ann Am Thorac Soc 2015 Sep 10. Epub ahead of print

32. Langton Hewer SC, Smyth AR. Antibiotic strategies for eradicating Pseudomonas aeruginosa in people with cystic fibrosis. Cochrane Database Syst Rev. 2014 Nov 10; 11: CD004197.

33. White L, Mirrani G, Grover M, Rollason J, Malin A, Suntharalingam J. Outcomes of Pseudomonas eradication therapy in patients with non-cystic fibrosis bronchiectasis. Respir Med 2012; 106: 356-360.

34. Orriols R, Hernando R, Ferrer A, Terradas S, Montoro B. Eradication Therapy against Pseudomonas aeruginosa in Non-Cystic Fibrosis Bronchiectasis. Respiration 2015; 90: 299-305.

35. McDonnell MJ, Jary HR, Perry A, MacFarlane JG, Hester KL, Small T, Molyneux C, Perry JD, Walton KE, De Soyza A. Non cystic fibrosis bronchiectasis: A longitudinal retrospective observational cohort study of Pseudomonas persistence and resistance. Respir Med 2015; 109: 716-726.

36. Brodt AM, Stovold E, Zhang L. Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review. Eur Respir J 2014; 44: 382-393.

37. Rosales-Mayor E, Serrano VA, Polverino E. Inhaled antibiotics in bronchiectasis. Community acquir infect 2015; 2: 8-12.

38. Wilson R, Welte T, Polverino E, De Soyza A, Greville H, O'Donnell A, Alder J, Reimnitz P, Hampel B. Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study. Eur Respir J 2013; 41: 1107-1115.

39. Gillham MI, Sundaram S, Laughton CR, Haworth CS, Bilton D, Foweraker JE. Variable

antibiotic susceptibility in populations of Pseudomonas aeruginosa infecting patients with bronchiectasis. J Antimicrob Chemother 2009; 63: 728-732.

40. Bilton D, Henig N, Morrissey B, Gotfried M. Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of Pseudomonas aeruginosa infection in adult bronchiectasis. Chest 2006; 130: 1503–1510.

41. Angrill J, Agustí C, de Celis R, Rañó A, Gonzalez J, Solé T, Xaubet A, Rodriguez-Roisin R, Torres A. Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. Thorax 2002;57: 15-19.

42. Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2012; 186: 657-665.

43. Purcell P, Jary H, Perry A, Perry JD, Stewart CJ, Nelson A, Lanyon C, Smith DL, Cummings SP, De Soyza A. Polymicrobial airway bacterial communities in adult bronchiectasis patients. BMC Microbiol 2014; 14: 130.

44. Maiz L, Vendrell M, Olveira C, Giron R, Nieto R, Martínez-Garcia MA. Prevalence and factors associated with isolation of Aspergillus and Candida from sputum in patients with non-cystic fibrosis bronchiectasis. Respiration 2015; 89: 396-403.

45. Bonaiti G, Pesci A, Marruchella A, Lapadula G, Gori A, Aliberti S. Nontuberculous Mycobacteria in Noncystic Fibrosis Bronchiectasis. Biomed Res Int 2015; 2015: 197950.

46. Vila J. “Fluoroquinolones resistance”. Chapter 4 from “Frontiers in antimicrobial resistance” by DG White, MN Alekshun and PF Mc Dermott

47. Hawkey PM. Mechanisms of quinolone action and microbial response. J Antimicrob

Chemother 2003; 51 Suppl 1: 29-35.

48. Band VI, Weiss DS. Mechanisms of Antimicrobial Peptide Resistance in Gram-Negative Bacteria. Antibiotics (Basel) 2015; 4: 18-41.

49. Stewart PS, Costerton JW. Antibiotic resistance of bacteria in biofilms. Lancet 2001; 358: 135-138.

50. Harbarth S, Samore MH. Antimicrobial resistance determinants and future control. Emerg Infect Dis 2005; 11: 794-801.

51. Levy SB. Antibiotic resistance: an ecological imbalance. Ciba Found Symp 1997; 207: 1-9.

52. Tay GT, Reid DW, Bell SC. Inhaled Antibiotics in Cystic Fibrosis (CF) and Non-CF Bronchiectasis. Semin Respir Crit Care Med 2015; 36: 267-286.

53. Vendrell M, de GJ, Olveira C, Martinez MA, Giron R, Maiz L, Canton R, Coll R, Escribano A, Sole A. Diagnosis and treatment of bronchiectasis. Spanish Society of Pneumology and Thoracic Surgery. Arch Bronconeumol 2008; 44: 629-640.

54. Woodhead M, Blasi F, Ewig S, Huchon G, Ieven M, Ortqvist A, Schaberg T, Torres A, van der HG, Verheij TJ. Guidelines for the management of adult lower respiratory tract infections. Eur Respir J 2005; 26: 1138-1180.

55. Canton R, Cobos N, de GJ, Baquero F, Honorato J, Gartner S, Alvarez A, Salcedo A, Oliver A, Garcia-Quetglas E. Antimicrobial therapy for pulmonary pathogenic colonisation and infection by Pseudomonas aeruginosa in cystic fibrosis patients. Clin Microbiol Infect 2005; 11: 690-703.

56. PROLONGED antibiotic treatment of severe bronchiectasis; a report by a subcommittee of the Antibiotics Clinical Trials (non-tuberculous) Committee of the Medical Research

Council. Br Med J 1957; 2: 255-259.

57. Delacourt C, Grimprel E, Cohen R. Antibiotic prophylaxis in pediatric pulmonology (excluding cystic fibrosis): which indications for rotating (or alternating) antibiotics and prolonged antibiotic therapy?. Arch Pediatr 2013; 20 Suppl 3: S99-103.

58. Evans DJ, Bara AI, Greenstone M. Prolonged antibiotics for purulent bronchiectasis in children and adults. Cochrane Database Syst Rev 2007; CD001392.

59. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Fergusson W, Tuffery C, Sexton P, Storey L, Ashton T. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet 2012; 380: 660-667.

60. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EH, Koppers RJ, van der Werf TS, Boersma WG. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 2013; 309: 1251-1259.

61. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, Biga S, Schlebusch S, Dash P, Bowler SD. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA 2013; 309: 1260-1267.

62. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. Lancet Respir Med 2013; 1: 262-274.

63. Fiel SB. Aerosolized antibiotics in cystic fibrosis: an update. Expert Rev Respir Med 2014; 8: 305-314.

64. Yang JW, Fan LC, Lu HW, Miao XY, Mao B, Xu JF. Efficacy and safety of long-term inhaled antibiotic for patients with noncystic fibrosis bronchiectasis: a meta-analysis. Clin Respir J 2015 Jan 26. doi: 10.1111/crj.12278. [Epub ahead of print].

65. Nicotra MB, Rivera M, Dale AM, Shepherd R, Carter R. Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. Chest 1995; 108: 955-961.

66. Kömüs N, Tertemiz KC, Akkoçlu A, Gülay Z, Yilmaz E.[Pseudomonas aeruginosa colonisation in bronchiectatic patients and clinical reflections]. Tuberk Toraks 2006; 54: 355-362.

67. Davies G, Wells AU, Doffman S, Watanabe S, Wilson R. The effect of Pseudomonas aeruginosa on pulmonary function in patients with bronchiectasis. Eur Respir J 2006; 28: 974-979.

68. Hill AT, Welham S, Reid K, Bucknall CE; British Thoracic Society. British Thoracic Society national bronchiectasis audit 2010 and 2011. Thorax 2012; 67: 928-930.

69. Murray MP, Govan JR, Doherty CJ, Simpson AJ, Wilkinson TS, Chalmers JD, Greening AP, Haslett C, Hill AT. A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2011; 183: 491-499.

70. Barker AF, Couch L, Fiel SB, Gotfried MH, Ilowite J, Meyer KC, O'Donnell A, Sahn SA, Smith LJ, Stewart JO, Abuan T, Tully H, Van Dalfsen J, Wells CD, Quan J. Tobramycin solution for inhalation reduces sputum Pseudomonas aeruginosa density in bronchiectasis. Am J Respir Crit Care Med 2000; 162: 481-485.

71. Drobnic ME, Suñé P, Montoro JB, Ferrer A, Orriols R. Inhaled tobramycin in non-cystic

fibrosis patients with bronchiectasis and chronic bronchial infection with Pseudomonas aeruginosa. Ann Pharmacother 2005; 39: 39-44.

72. Haworth CS, Foweraker JE, Wilkinson P, Kenyon RF, Bilton D. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. Am J Respir Crit Care Med 2014; 189: 975-982.

73. Barker AF, O'Donnell AE, Flume P, Thompson PJ, Ruzi JD, de Gracia J, Boersma WG, De Soyza A, Shao L, Zhang J, Haas L, Lewis SA, Leitzinger S, Montgomery AB, McKevitt MT, Gossage D, Quittner AL, O'Riordan TG. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. Lancet Respir Med 2014; 2: 738-749.

74. Rogers GB, Bruce KD, Martin ML, Burr LD, Serisier DJ. The effect of long-term macrolide treatment on respiratory microbiota composition in non-cystic fibrosis bronchiectasis: an analysis from the randomised, double-blind, placebo-controlled BLESS trial. Lancet Respir Med 2014; 2: 988-996.

75. Renna M, Schaffner C, Brown K, Shang S, Tamayo MH, Hegyi K, Grimsey NJ, Cusens D, Coulter S, Cooper J, Bowden AR, Newton SM, Kampmann B, Helm J, Jones A, Haworth CS, Basaraba RJ, DeGroote MA, Ordway DJ, Rubinsztein DC, Floto RA. Azithromycin blocks autophagy and may predispose cystic fibrosis patients to mycobacterial infection. J Clin Invest 2011; 121: 3554-3563.

76. Aksamit TR, Philley JV, Griffith DE. Nontuberculous mycobacterial (NTM) lung disease: the top ten essentials. Respir Med 2014; 108: 417-425.

77. Coolen N, Morand P, Martin C, Hubert D, Kanaan R, Chapron J, Honoré I, Dusser D,

Audureau E, Veziris N, Burgel PR. Reduced risk of nontuberculous mycobacteria in cystic fibrosis adults receiving long-term azithromycin. J Cyst Fibros 2015; 14: 594-599.

78. Schembri S, Williamson PA, Short PM, Singanayagam A, Akram A, Taylor J, Singanayagam A, Hill AT, Chalmers JD. Cardiovascular events after clarithromycin use in lower respiratory tract infections: analysis of two prospective cohort studies. BMJ 2013; 346: f1235.

79. Maisch NM, Kochupurackal JG, Sin J. Azithromycin and the risk of cardiovascular complications. J Pharm Pract 2014; 27: 496-500.

80. Chalmers JD, McHugh BJ, Doherty C, Smith MP, Govan JR, Kilpatrick DC, Hill AT. Mannose-binding lectin deficiency and disease severity in non-cystic fibrosis bronchiectasis: a prospective study. Lancet Respir Med 2013; 1: 224-232.

81. Chalmers JD, Fleming GB, Hill AT, Kilpatrick DC. Impact of mannose-binding lectin insufficiency on the course of cystic fibrosis: A review and meta-analysis. Glycobiology 2011; 21: 271-282.

82. Fothergill JL, Walshaw MJ, Winstanley C. Transmissible strains of Pseudomonas aeruginosa in cystic fibrosis lung infections. Eur Respir J 2012; 40: 227-238.

83. De Soyza A, Perry A, Hall AJ, Sunny SS, Walton KE, Mustafa N, Turton J, Kenna DT, Winstanley C. Molecular epidemiological analysis suggests cross-infection with Pseudomonas aeruginosa is rare in non-cystic fibrosis bronchiectasis. Eur Respir J 2014; 43: 900-903.

84. Al-Aloul M, Crawley J, Winstanley C, Hart CA, Ledson MJ, Walshaw MJ. Increased morbidity associated with chronic infection by an epidemic Pseudomonas aeruginosa

strain in CF patients. Thorax 2004; 59: 334-336.

85. Fothergill JL, Mowat E, Ledson MJ, Walshaw MJ, Winstanley C. Fluctuations in phenotypes and genotypes within populations of Pseudomonas aeruginosa in the cystic fibrosis lung during pulmonary exacerbations. J Med Microbiol 2010; 59: 472-481.

86. Altenburg J, de Graaff CS, van der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics - part 2: advantages and disadvantages of long-term, low-dose macrolide therapy. Respiration 2011; 81: 75-87.

87. O'Donnell AE. Bronchiectasis. Chest 2008; 134: 815-823.

88. Zanini A, Aiello M, Adamo D, Cherubino F, Zampogna E, Sotgiu G, Chetta A, Spanevello A. Effects of Pulmonary Rehabilitation in Patients with Non-Cystic Fibrosis Bronchiectasis: A Retrospective Analysis of Clinical and Functional Predictors of Efficacy. Respiration 2015; 89: 525-533.

89. Hester K, McAlinden P, De Soyza A. Education and information for patients with bronchiectasis: What do patients want? Eur Respir J 2011; 38: 3622.

90. McCullough A, Tunney MM, Elborn JS, Bradley JM, Hughes CM. All illness is personal to that individual': a qualitative study of patients' perspectives on treatment adherence in bronchiectasis. Health Expectations 2014 Jun 20. doi: 10.1111/hex.12217. [Epub ahead of print].

91. Baggott CJ , Harris E, Suntharalingam J, Malin AS. P95 Non Cf Bronchiectasis: Smoothing the process: clinical management of COPD and bronchiectasis. Thorax 2014; 69: A118-A119.

EXAMPLE OF PATIENTS'QUESTIONNAIRE

Help shape the future of bronchiectasis research and treatment across Europe

We are asking people with bronchiectasis, their families and friends to tell us what we should be looking at to provide answers to the challenges of treating and living with bronchiectasis.
What do YOU think needs to change or be considered to have the greatest impact on quality of life for people with bronchiectasis?
This survey is part of the work of EMBARC (European Multicentre Bronchiectasis Audit and Research Collaboration) to facilitate multidisciplinary collaborative research in non-cystic fibrosis bronchiectasis (www.bronchiectasis.eu).
EMBARC is currently working on an action plan that describes what is needed to reduce the impact of bronchiectasis on you and on healthcare systems in Europe. Your answers will influence what research is done by these research centres in future.
This survey will take up to 15 minutes to complete, and is anonymous. If you would like to receive updates or would like to become more involved in the project, you can enter your email address at the end of the survey.

1. Are you…? A person with bronchiectasis A parent, relative or carer of someone with bronchiectasis Other (please specify)

2. What age are you?
   Under 18
   18-30
   31-50
   51-60
   61-70
   Over 70

3. Are you..?
   Male
   Female

4. In which country do you live?

5. What aspect of your / your partner or relative's bronchiectasis do you/they find the most difficult to manage?

	Not an issue	Not very difficult	Difficult	Very difficult	No opinion
Cough					
Sputum (mucus/phlegm from the lungs)					
Coughing up blood					
Shortness of breath					
Not feeling fit or having the strength to do daily activities, such as walking far, doing housework, shopping, hobbies					
Tiredness					
Sleeping problems					
Weight loss					
Anxiety					
Depression					
Fever					
Exacerbations (episodes of increased sputum (mucus) or					

change in its colour, new or increased shortness of breath and/or fever that lead you to go to the doctor)					
Emergency hospital admission					
Other (please specify)					

6. To manage bronchiectasis well it is important to understand the disease. How important do you think the following areas of research are to improve how bronchiectasis is managed by doctors?

	Unimportant	Not very important	Important	Very important	No opinion
To identify how often and why bronchiectasis occurs in certain groups of people across Europe					
To identify the cause(s) of bronchiectasis					
To identify how bronchiectasis develops and continues					
To identify what makes some patients' bronchiectasis get worse					
To understand the relationship between bronchiectasis and other medical conditions, such as asthma, 'acid' reflux, inflammatory bowel diseases					
To explore the link between getting a cold (for example rhinovirus) and having an exacerbation To identify triggers for an exacerbation					
To identify triggers for an exacerbation					
To find ways to diagnose bronchiectasis earlier, such as by local doctors					
Testing new techniques for managing bronchiectasis in real world environments, such as at home and community settings (not in the laboratory or in hospitals)					

7. Each person's bronchiectasis can affect them differently. This makes it difficult to know which is the best treatment. How important do you think the following areas are to help improve how bronchiectasis is treated?

	Unimportant	Not very important	Important	Very important	No opinion
To develop better ways of teaching people to use their medicines					
To develop medicines that can be taken in different ways, such as for inhaled or nebulised					
Using longer-term antibiotic therapy when a person's condition is stable					
Using vaccines to prevent exacerbations					
Knowing more about the role of physiotherapy and pulmonary rehabilitation (a short course of regular exercise sessions and education sessions)					
Educating primary care doctors to prescribe the same dose/length of antibiotic therapy for exacerbations in bronchiectasis as used in cystic fibrosis					
To improve awareness of bronchiectasis in community care services, for example among community-based nurses and physiotherapists					

8. Bronchiectasis is such a complex condition that there is currently no agreed best way to look for changes. How important do you think the following areas are to improve how each person's bronchiectasis is monitored?

	Unimportant	Not very important	Important	Very important	No opinion
Having regular lung function testing to help notice changes or increased risk of an exacerbation					
Having the equipment at home to					

monitor symptoms					
Having regular computed tomography (CT) scans to look for changes or increased risk of an exacerbation					
Regular sputum examinations when a person is stable and during an exacerbation to learn more about how the condition changes					
Being able to monitor and treat the coughing up of blood					
Being able to identify people at increased risk of poor outcomes or needing urgent treatment for their bronchiectasis					

9. Education, technology and self-awareness, known as self-management, can help each person gain greater control over their bronchiectasis by reducing exacerbations and improving how well they feel. How important do you think the following areas are in improving self-management throughout life?

	Unimportant	Not very important	Important	Very important	No opinion
Good communication between healthcare professionals and each person with bronchiectasis					
Having a self-management programme and care plan designed with each person to help them have greater control over their condition and recognise/manage an exacerbation					
Ensuring each person has access to a home intravenous (IV) antibiotic service to avoid unnecessary hospital admissions					
Using peer support forums and social media to exchange information with others					
Providing each person with copies of their test results so they can keep a					

useful history of the progress of their own condition					
Having access to reliable, easy to understand information about different aspects of living with bronchiectasis					
Having access to physiotherapy and being taught the techniques and how to use the equipment at home					

10. Are there any other areas that you think should be researched in the field of bronchiectasis?

11. If you would like to receive updates on the project or get involved and represent others with bronchiectasis, please enter your email address.

If you have any comments or questions, email Sarah Masefield (sarah.masefield@europeanlung.org) at the European Lung Foundation (ELF). Thank you very much for your time and participation in this project.