CHEST

US Patient-Centered Research Priorities and Roadmap for Bronchiectasis

Emily Henkle, PhD, MPH; Timothy R. Aksamit, MD; Charles L. Daley, MD; David E. Griffith, MD; Anne E. O'Donnell, MD; Alexandra L. Quittner, PhD; Elisha Malanga, BS; Delia Prieto, MSEd; Amy Leitman, JD; and Kevin L. Winthrop, MD, MPH

Noncystic fibrosis bronchiectasis (bronchiectasis) is an increasingly common chronic lung disease that is difficult to manage because of a lack of evidence on which to base treatment decision-making. We sought to develop a practical list of US-based patient-centered research priorities and an associated roadmap to guide bronchiectasis research. We designed and administered a web-based patient needs assessment survey to establish broad research priorities, convened three stakeholder webinars to confirm the top priorities, obtained written stakeholder feedback, and completed a final consensus survey of objectives. The stakeholder panel consisted of clinical research experts in bronchiectasis, a seven-member patient advisory panel, and representatives from the two key patient advocacy organizations: COPD Foundation and NTM Info and Research Inc. Based on survey results from 459 patients with bronchiectasis, the stakeholder panel identified 27 patient-centered research priorities for bronchiectasis in the areas of bronchiectasis treatment and prevention of exacerbations, improving treatment of exacerbations and infections, improving health-related quality of life, predictors of poor prognosis, understanding the impact of underlying conditions, and conducting patient-centered clinical trials. These priorities should further inform the development and evaluation of both new and previously unproven therapies, with particular attention to the inclusion of patient-reported outcomes. We anticipate a great deal of progress will be made in the field of bronchiectasis in the next decade. CHEST 2018; 154(5):1016-1023

KEY WORDS: bronchiectasis; disease progression; drug therapy; health-related quality of life; infection

Bronchiectasis is a chronic, inflammatory airway disease that has a marked impact on health-related quality of life (HRQoL). Although this diagnosis is associated with cystic fibrosis (CF), most patients do not have CF and represent a heterogeneous group of patients termed non-CF bronchiectasis (bronchiectasis). Bronchiectasis predominantly affects women and incidence increases with age, with most patients > 65 years of age. Bronchiectasis has likely surpassed the rare disease threshold

ABBREVIATIONS: BSI = Bronchiectasis Severity Index; CF = cystic fibrosis; EMBARC = European Multicentre Bronchiectasis Audit and Research Collaboration; HRQoL = health-related quality of life; NTM = nontuberculous mycobacteria; NTMir = NTM Info and Research Inc; QOL-B = Quality of Life-Bronchiectasis instrument

AFFILIATIONS: From the OHSU-PSU School of Public Health (Drs Henkle and Winthrop), Portland, OR; Pulmonary Disease and Critical Care Medicine (Dr Aksamit), Mayo Clinic, Rochester, MN; the Division of Mycobacterial and Respiratory Infections (Dr Daley), National Jewish Health, Denver, CO; University of Texas at Tyler (Dr Griffith), Tyler, TX; Georgetown University Medical Center (Dr O'Donnell), Washington, DC; Nicklaus Children's Research Institute (Dr Quittner), Miami, FL; COPD Foundation (Mss Malanga and Prieto), Miami, FL; NTM Info & Research (Ms Leitman), Coral Gables, FL; and the Department of Infectious Disease (Dr Winthrop), OHSU School of Medicine, Portland, OR.

FUNDING/SUPPORT: This study was funded by a Patient-Centered Outcomes Research Institute Eugene Washington Engagement Award [Contract 2651-OHSU].

CORRESPONDENCE TO: Emily Henkle, PhD, MPH, 3181 SW Sam Jackson Park Rd, Mailcode GH104, Portland, OR 97239; e-mail: henkle@ohsu.edu

DOI: https://doi.org/10.1016/j.chest.2018.06.032

with > 200,000 adults currently living with bronchiectasis in the United States.[1-3]

Bronchiectasis is characterized by a cycle of airway infection, inflammation, and progressive airway injury leading to irreversible bronchial tube dilation and propagation of additional airway infection, inflammation, and injury.[4] Chronic infections with *Pseudomonas aeruginosa* and nontuberculous mycobacteria (NTM) are commonly associated with the diagnosis. There are now several international expert-guided treatment summaries and recommendations.[5-7] These guidelines highlight the need for research in many aspects of this disease.

As large, comprehensive patient registries are developed in the United States, Europe, and Australia, there is a need to align data collection with key research priorities. In addition, a number of new therapies are in development. One new area in clinical trial design is the use of patient-reported outcomes, such as measures of HRQoL. The European Multicentre Bronchiectasis Audit and Research Collaboration (EMBARC) published a consensus statement of 22 recommendations based on 55 expert research priorities and 29 patient research priorities in mid-2016.[8] With input from a range of patient and clinical stakeholders, we sought to develop a concise, patient-centered US bronchiectasis research roadmap, to provide essential direction for future bronchiectasis research.

Roadmap Development

The US bronchiectasis patient-centered research priorities and roadmap (roadmap) was developed over the course of 1 year and completed in 2017. The roadmap was generated using a web-based needs assessment survey to establish broad research priorities, three stakeholder webinars, written stakeholder feedback on the roadmap, and a final consensus survey of objectives ranked as high, moderate, neutral, low, or not a priority. The 23-member stakeholder panel included clinical research experts in bronchiectasis with representatives from the US Bronchiectasis Research Consortium, a seven-member patient advisory panel, and representatives from two key patient advocacy organizations: COPD Foundation and NTM Info and Research Inc (NTMir).

The anonymous needs assessment survey was developed using SurveyMonkey (e-Appendix 1). The survey captured basic information about age, sex, geographic location, and underlying diagnoses. Next, respondents were asked to select their top three priority areas for bronchiectasis research (including an open-ended "other") and the single top priority from the following topic areas: diagnosis, prognosis, therapy, quality of life, health communication, and data sources and analysis. There was also an opportunity to include an open-ended response to other topics in need of further research. Last, they were specifically asked about their top three outcomes for bronchiectasis therapy studies.

The survey was open May through mid-November 2016. During the project, a new COPD Foundation Bronchiectasis and NTM Initiative website was launched, inviting patients, caregivers, and clinicians to join the bronchiectasis community: BronchandNTM360social (www.BronchandNTM360social.org). Information about the roadmap development and direct links to the survey were posted on the website. In addition, patients with bronchiectasis were invited to complete the survey via letters to the U.S. Bronchiectasis and NTM Research Registry participants (N = 2,200), e-mail blasts from our partners and the COPD Foundation and NTMir, and inclusion of the website and needs assessment survey link in the COPD Digest (now an online publication) and COPD Foundation e-newsletter, which reach 140,000 and 40,000 people with COPD, respectively, some of whom also have bronchiectasis.

Needs Assessment Survey Respondents

Overall, the survey patient population (N = 459 with a self-reported diagnosis of bronchiectasis) reflects the general population with bronchiectasis. Most (70%) were between 50 and 79 years old and 87% were women; 17% reported no listed underlying condition, 25% reported a COPD diagnosis, 20% reported a genetic condition (other than CF) predisposing them to bronchiectasis, and 56% reported any current or history of NTM.

Research Priorities and Objectives

A total of 27 objectives in six priority areas were selected based on survey results and stakeholder discussion (Table 1). The survey results within each priority area are subsequently described and listed in no particular order, with a discussion included in each section.

Priority 1: Improve Treatment of Bronchiectasis and Prevent Exacerbations

Over 75% of survey responders selected treatment of bronchiectasis as one of their top three research priorities. When limited to a single therapeutic priority, 52% selected bronchiectasis treatment and 14% selected complementary or alternative therapy. Prevention of

TABLE 1] US Patient-Centered Bronchiectasis Research Priorities and Objectives

Priority	Objectives	Consensus rating
1. Improve treatment of bronchiectasis and prevent exacerbations	1.1. Rigorously evaluate the efficacy and safety of long term use of inhaled corticosteroids in bronchiectasis.	Very high priority
	1.2. Evaluate the efficacy and safety of inhaled antibiotics to prevent exacerbations.	Very high priority
	1.3. Compare the effectiveness of physical airway clearance techniques, accounting for patient preference and adherence, e.g. vibratory positive expiratory pressure, percussion therapy/ chest physiotherapy.	High priority
	1.4. Evaluate the efficacy of mucolytics and hypertonic saline in bronchiectasis.	High priority
	1.5. Evaluate the efficacy of bronchodilators in bronchiectasis.	Moderate priority
	1.6. Evaluate naturopathic and alternative therapies to reduce inflammation.	Moderate priority
2. Improve treatment of exacerbations and associated infections	2.1. Update treatment guidelines for chronic co-infections with pathogens including NTM.	Very high priority
	2.2. Establish a standardized definition of exacerbation of bronchiectasis.	High priority
	2.3. Evaluate the optimal duration of antibiotics for the treatment of acute infectious exacerbations of bronchiectasis.	High priority
	2.4. Establish updated and more broadly applicable guidelines to the approach of acute exacerbations of bronchiectasis.	High priority
	2.5. Evaluate the role of culture of respiratory secretions at baseline and during exacerbations on the impact of response to antibiotics and clinical outcomes.	High priority
	2.6. Explore the impact of specific elements of symptoms and signs of exacerbations on the sensitivity and specificity of exacerbation definition.	Moderate priority
	2.7. Evaluate the utility of *in vitro*/*in vivo* antibiotic susceptibility testing for guiding antibiotic treatment regimens.	Moderate priority
3. Improve health-related quality of life	3.1. Consider time and ease of administration in the development of new drugs.	High priority
	3.2. Measure the efficacy of new pharmaceutical and complementary treatments including acupuncture, exercise, diet, massage, relaxation training, and yoga/ mindfulness.	Moderate priority
4. Identify predictors of poor prognosis	4.1. Develop a disease activity score that takes into account subjective patient-reported outcomes.	High priority
	4.2. Identify biomarker candidates.	High priority
	4.3. Develop and evaluate biomarkers that can be used as predictors of poor prognosis.	High priority
	4.4. Validate the BSI in the U.S. in a more diverse bronchiectasis population including Asian patients and those with NTM disease.	Moderate priority
	4.5. Validate the BSI as a predictor of exacerbations.	Moderate priority
	4.6. Evaluate the utility of BSI as a clinical tool to guide therapeutic choice.	Moderate priority
5. Understand impact of underlying conditions	5.1. Describe the natural history of bronchiectasis in patients with different underlying and concomitant diagnoses.	High priority
	5.2. Conduct subgroup analyses where possible to identify differences in treatment response or risks.	Moderate priority

(Continued)

TABLE 1] *(Continued)*

Priority	Objectives	Consensus rating
6. Conduct patient-centered clinical trials	6.1 Evaluate the correlation between health-related quality of life measures and treatment response.	Very high priority
	6.2 Include the NTM module for those with bronchiectasis and NTM.	High priority
	6.3 Include the QOL-B as a primary or secondary outcome measure within all bronchiectasis clinical trials.	High priority
	6.4 Involve patients in the design of clinical trials for bronchiectasis.	High priority

Consensus rating, average stakeholder score on a 5 point scale: 3.0-<4.0 = Moderate, 4.0-<4.5 = High, ≥4.5 = Very high. BSI = Bronchiectasis severity index[28]; NTM = nontuberculous mycobacterium; QOL-B = Quality of life-bronchiectasis.[24]

exacerbations was the second most commonly selected research priority, selected as one of the top three priorities by 54% of survey respondents.

Clinicians often recommend airway clearance devices, presenting patients with the various device options and working with patients to determine which works best for them without evidence of comparative effectiveness.[5] A number of untested or unproven pharmacotherapies (eg, steroids, bronchodilators, hypertonic saline, others) are also routinely used to treat patients with bronchiectasis.[9,10] Suppressive antibiotics, including inhaled tobramycin, gentamicin, aztreonam, and colistin, are used off-label for patients with bronchiectasis to prevent acute infectious exacerbations. However, to date statistically significant evidence of a benefit for inhaled antibiotics in patients with bronchiectasis remains elusive. Two phase 3 randomized placebo-controlled clinical trials of inhaled aztreonam did not provide benefits in patients with bronchiectasis.[11] Results from phase 3 randomized clinical trial programs of two different formulations of inhaled ciprofloxacin (dry powder and liposomal) reported mixed results.[12-14] Other important areas for further research include the optimal duration and dosing schedules for suppressive antibiotics given to reduce bacterial burden. Whether a 28-day on/off cycle, 14-day on/off cycle, or continuous delivery is optimal is equally unclear. More recently, oral macrolide use for immunomodulatory purposes has been shown to reduce frequency of exacerbations.[15-17] However, the durability of effect and potential impact on treating associated infections including NTM and other pathogens remains uncertain.

Priority 2: Improve Treatment of Exacerbations and Associated Infections

Treatment of infections (50% of survey respondents) and exacerbations (44% of survey respondents) were the third and fourth ranked research priorities. Among bronchiectasis treatment priorities, 33% of survey respondents selected treatment of exacerbations or associated infections as the top priority. Acute infectious exacerbations may occur several times per year. However, the nature of acute exacerbations has not been rigorously studied. Until recently, the definition of an acute exacerbation of bronchiectasis has varied across clinical trials and among clinicians. In 2017, a global consensus definition of bronchiectasis exacerbation was published to improve clinical research design and allow comparison across studies.[18]

The airways are home to diverse communities of microbiologic organisms, and this microbiome of the normal airway changes in patients with bronchiectasis.[19,20] What remains unknown is how best to approach this microbiology in the context of antibiotic treatment selection during an acute exacerbation. The presence of *P aeruginosa* in respiratory secretions is associated with increased symptoms, accelerated loss of lung function, and more frequent exacerbations.[21,22] Whether other organisms isolated at the time of exacerbation have similar effects on prognosis is unclear. In addition, the treatment of chronic coinfections such as NTM or fungi (eg, *Aspergillus* species) that can cause decline is important. NTM treatment guidelines have been published and are in the process of being updated.[23] However, the role of these chronic coinfections on the approach to treatment of acute exacerbations because of other organisms is not clear.

Priority 3: Improve HRQoL

Bronchiectasis has a major impact on patients' HRQoL. It is a chronic, progressive disease that must be managed because it is only rarely cured (when localized) with surgery. The symptom burden associated with bronchiectasis is significant and can interfere with daily

activities and physical, social, and emotional functioning. Chronic respiratory symptoms, such as cough and sputum production, can be hard to manage in social situations and can cause fatigue and difficulties with sleep. Most individuals spend 60 to 120 min/d on airway clearance and inhaled medication treatments. The top two priorities for survey respondents in relation to HRQoL were reducing the impact of the disease on daily life (54%) and reducing treatment burden (28%).

The stakeholder panel identified several ways to reduce treatment burden. One is to develop devices that shorten treatment time. For example, the tobramycin inhalation powder device decreases treatment time from 40 min/d to about 5 min. Another way to reduce burden is to simplify administration of the medication. The tobramycin inhalation powder device consists of disposable capsules with no need to clean or sanitize equipment. This device is also portable so that people can travel more easily. The validated Quality of Life-Bronchiectasis instrument (QOL-B) patient-reported outcome survey has a treatment burden scale which can be used to measure whether a new mode of administration reduces burden.[24] The US Food and Drug Administration and European Medicines Agency now accept patient-reported outcomes as evidence of efficacy, particularly scales that measure key symptoms (eg, improvement in respiratory symptoms), and the QOL-B includes a respiratory symptoms scale.

Priority 4: Identify Predictors of Poor Prognosis

Bronchiectasis is diagnosed by findings on a high-resolution CT scan. After diagnosis, survey respondents were most interested in measuring disease severity and improving provider education about bronchiectasis. Clinician education about bronchiectasis applies across all priorities and will be addressed in the discussion. In terms of prognosis, 45% of survey respondents selected biomarkers (items in your blood that indicate more rapidly progressing disease or higher risk for complications) as the top priority and 25% prioritized severity measures. Biomarkers and severity measures were combined as predictors of poor prognosis in this section.

A biomarker that predicts poor prognosis can be used in the clinical setting to identify patients who may benefit from therapy, measure drug toxicity, or include as a surrogate end point in clinical trials. Given the inflammatory nature of this disease, it is possible that inflammatory markers alone or in combination with clinical findings could be used as a measure of disease activity. Currently, there are no widely accepted biomarkers for disease severity or progression in bronchiectasis. However, recent studies have documented that sputum neutrophil elastase correlated with both disease severity and disease progression in patients with CF[25,26] and without CF.[27] Because higher neutrophil elastase levels were associated with lung function decline and exacerbations, they may be useful as surrogate markers in clinical trials.

Several tools have been developed in Europe to measure disease severity: the Bronchiectasis Severity Index (BSI) and the FACED score.[28,29] In a multicenter pooled analysis, the BSI was consistently a better predictor of death, objective clinical outcomes (ie, hospital admissions, exacerbations, lung function decline), and HRQoL measured by the QOL-B.[30] Further evaluation of the BSI tool is needed in a US population, which is more racially diverse, and regarding underlying and associated conditions, including NTM disease.[1]

Priority 5: Understand the Impact of Underlying Conditions

The stakeholder panel also selected improving our understanding of underlying diagnoses (21% selected as their top priority) from the general category of prognosis. We have already distinguished patients with bronchiectasis associated with CF with those without. In fact, bronchiectasis is associated with a number of underlying conditions that cause the development of bronchiectasis; however, in many cases it is considered idiopathic with no detectable underlying cause.

Common conditions that impact bronchiectasis diagnosis and treatment include COPD and asthma. Some of the most important rare causes of bronchiectasis include allergic bronchopulmonary aspergillosis, pulmonary ciliary dyskinesia, immune deficiency (eg, common variable immune deficiency), autoimmune disorders (eg, Sjogren syndrome, rheumatoid arthritis), and Marfan disease. In the absence of diagnostic criteria for CF, heterozygosity of CF transmembrane conductance regulator mutations may play a role in the development of bronchiectasis. Diagnosis and treatment of these and other underlying conditions is part of standard of care for patients with bronchiectasis. What is unclear is whether there are differences in treatment and prognosis, and how to prevent bronchiectasis development and progression.[31]

Priority 6: Conduct Patient-Centered Clinical Trials

Modern research is increasingly being conducted with patient partners. The US Food and Drug Administration

Patient-Focused Drug Development initiative is gathering input from patients and clinical experts on 20 diseases. Funding agencies, including the Patient-Centered Outcomes Research Institute, increasingly require patients to be involved in study development and clinical trial recruitment as stakeholders. The purpose is to conduct meaningful clinical research to answer questions most relevant to patients. Patient input has the potential to help clinical trials evolve to a stage where they present data more reflective of real-world impact on the patients themselves. Several public documents and meetings have noted patient input on the design of clinical trials for patients with bronchiectasis and the related comorbidities which result from the underlying illness.[32,33]

The QOL-B is a validated, modern tool to collect patient-reported outcomes for bronchiectasis.[24,34] The Cystic Fibrosis Questionnaire-Revised, a similar tool which measures HRQoL in patients with CF, is a standard end point in clinical trials for CF. In the two phase 3 randomized trials that used the QOL-B as a primary outcome, the physical functioning score was highly associated with lung function (FEV_1) at baseline.[11] Slower 6-min walk tests were associated with lower scores for physical functioning, vitality, role functioning, and health perceptions in both studies, and respiratory symptoms and emotional functioning in one study. Given the impact of bronchiectasis on HRQoL, we support the expanded use of QOL-B as a key patient-reported outcome for clinical trials, with the use of appropriate analytic methods. For patients with both bronchiectasis and NTM, a complementary NTM symptom module has been developed, and final validation is expected in 2018.[35]

Discussion

The US patient and clinical research expert stakeholder panel identified 27 patient-centered research priorities for bronchiectasis in the areas of treatment and prevention of exacerbations, improving treatment of exacerbations and infections, improving HRQoL, predictors of poor prognosis, understanding the impact of underlying conditions, and conducting patient-centered clinical trials. Overall, the priorities in the United States were similar to those identified by EMBARC.[8] The EMBARC statement included 22 recommendations and rankings of 84 expert and patient priorities, many of which were related to *P aeruginosa* colonization and eradication, which were not specifically highlighted in the US priorities. The focus on patient-centered clinical trials, involving patients in the design of these studies, was unique to the US priorities. Our stakeholder panel included key advocacy and research organizations in the United States, NTMir, the COPD Foundation, and the Bronchiectasis Research Consortium.

The stakeholder panel agreed on several specific next steps as a roadmap to ensure that progress is made on the objectives outlined here. The first is to expand data sources and analysis to better understand the natural history of bronchiectasis and conduct research in the United States. In response to feedback from the Bronchiectasis Research Consortium and industry partners, the Bronchiectasis Research Registry has been expanded. However, there is still a need to collect patient-reported data and biologic samples in the Bronchiectasis Research Registry. The second is improved tools and evidence are needed to make informed treatment decisions. This means increasing the number of bronchiectasis clinical trials, improving the understanding of lung microbiome, collection of biologic samples alongside a registry, and developing evidence-based clinical management guidelines that are applicable in the United States. The third is increasing the awareness of bronchiectasis and developing resources for general practitioners and patients. In our needs assessment survey, 36% of respondents selected need for patient information as the top priority for communication about bronchiectasis. The COPD Foundation and NTMir are already working closely with patients and researchers to fill these gaps in bronchiectasis education and information and have formed a centralized online community of patients with bronchiectasis online (www.BronchandNTM360social.org).

Given the goals of therapy involve maintaining HRQoL and minimizing disease progression, and currently, there is routine use of several untested or unproven therapies, we think both prioritizing research questions and studying outcomes of interest to patients will provide the most efficient progress in caring for patients with this disease. In conclusion, the field of bronchiectasis research is underdeveloped to date, even as the disease has become increasingly common.

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: T. R. A. has participated in clinical trials sponsored by Bayer, Aradigm, and Insmed but has not received any personal or research support. C. L. D. received research support from

Insmed. D. E. G. has received support as a consultant for Aradigm/Grifols and has received grant support from Insmed. A. E. O. is a principal investigator/received grant support for clinical trials for Aradigm, Bayer, and Insmed and is a consultant for Bayer, Novartis, and Xellia Pharmaceuticals. A. L. Q. has served as a consultant to Bayer and Aradigm and has received grant support from Insmed. K. L. W. has served as a consultant to Bayer and has received grant support from Insmed. None declared (E. H., E. M., D. P., A. L.).

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript. The views and statements in this manuscript are solely the responsibility of the authors and do not necessarily represent the views of the Patient-Centered Outcomes Research Institute, its Board of Governors, or its Methodology Committee.

Other contributions: We thank the Patient Advisory Panel (Cynthia Flora, MEM, Tim Foster, Barbara Hudson, JD, Michael Kitson, Mary Kitlowski, Beth McKnight, and Margery Stalch) and additional stakeholders from OHSU (Megan Wardrop, MS), the COPD Foundation (William Clark, Peter Amari, Vincent Malanga, Gretchen McCreary, MA, and David Mannino, MD), and NTM Info and Research Inc (Philip Leitman).

Additional information: The e-Appendix can be found in the Supplemental Materials section of the online article.

References

1. Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots R. Trends in bronchiectasis among medicare beneficiaries in the United States, 2000 to 2007. *Chest*. 2012;142(2):432-439.
2. O'Donnell AE. Bronchiectasis. *Chest*. 2008;134(4):815-823.
3. Weycker D, Hansen GL, Seifer FD. Prevalence and incidence of noncystic fibrosis bronchiectasis among US adults in 2013. *Chron Respir Dis*. 2017;14(4):377-384.
4. McShane PJ, Naureckas ET, Strek ME. Bronchiectasis in a diverse US population: effects of ethnicity on etiology and sputum culture. *Chest*. 2012;142(1):159-167.
5. Pasteur MC, Bilton D, Hill AT. British Thoracic Society Bronchiectasis non-CF Guideline Group. British Thoracic Society guideline for non-CF bronchiectasis. *Thorax*. 2010;65(suppl 1):i1-i58.
6. Martinez-Garcia MA, Maiz L, Olveira C, et al. Spanish guidelines on treatment of bronchiectasis in adults. *Arch Bronconeumol*. 2018;54(2):88-98.
7. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. *Eur Respir J*. 2017;50(3).
8. Aliberti S, Masefield S, Polverino E, et al. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. *Eur Respir J*. 2016;48(3):632-647.
9. Aksamit TR, O'Donnell AE, Barker A, et al. Adult patients with bronchiectasis: a first look at the US Bronchiectasis Research Registry. *Chest*. 2017;151(5):982. 992.
10. Henkle E, Aksamit TR, Barker AF, et al. Pharmacotherapy for non-cystic fibrosis bronchiectasis: results from an NTM Info & Research Patient Survey and the Bronchiectasis and NTM Research Registry. *Chest*. 2017;152(6):1120-1127.
11. Barker AF, O'Donnell AE, Flume P, et al. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. *Lancet Respir Med*. 2014;2(9):738-749.
12. Aksamit T, De Soyza A, Bandel TJ, et al. RESPIRE 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur Respir J*. 2018;51(1).
13. De Soyza A, Aksamit T, Bandel TJ, et al. RESPIRE 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. *Eur Respir J*. 2018;51(1).
14. Haworth CS, Wanner A, Froelich J, O'Neal T, Davis A, Gonda I, O'Donnell A, editors. Inhaled liposomal ciprofloxacin in patients with bronchiectasis and chronic pseudomonas aeruginosa infection: results from two parallel phase III Trials (ORBIT-3 and -4) American Thoracic Society 2017; Washington, DC. Am J Respir Crit Care Med. 2017;195:A7604.
15. Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. *JAMA*. 2013;309(12):1251-1259.
16. Serisier DJ, Martin ML, McGuckin MA, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. *JAMA*. 2013;309(12):1260-1267.
17. Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):660-667.
18. Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. *Eur Respir J*. 2017;49(6).
19. Dickson RP, Martinez FJ, Huffnagle GB. The role of the microbiome in exacerbations of chronic lung diseases. *Lancet*. 2014;384(9944):691-702.
20. Tunney MM, Einarsson GG, Wei L, et al. Lung microbiota and bacterial abundance in patients with bronchiectasis when clinically stable and during exacerbation. *Am J Respir Crit Care Med*. 2013;187(10):1118-1126.
21. Wilson CB, Jones PW, O'Leary CJ, Hansell DM, Cole PJ, Wilson R. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. *Eur Respir J*. 1997;10(8):1754-1760.
22. Chalmers JD, Aliberti S, Filonenko A, et al. Characterisation of the "frequent exacerbator phenotype" in bronchiectasis. *Am J Respir Crit Care Med*. 2018;197(11):1410-1420.
23. Griffith DE, Aksamit T, Brown-Elliott BA, et al. An official ATS/IDSA statement: diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases. *Am J Respir Crit Care Med*. 2007;175(4):367-416.
24. Quittner AL, O'Donnell AE, Salathe MA, et al. Quality of Life Questionnaire-Bronchiectasis: final psychometric analyses and determination of minimal important difference scores. *Thorax*. 2015;70(1):12-20.
25. Mayer-Hamblett N, Aitken ML, Accurso FJ, et al. Association between pulmonary function and sputum biomarkers in cystic fibrosis. *Am J Respir Crit Care Med*. 2007;175(8):822-828.
26. Sagel SD, Wagner BD, Anthony MM, Emmett P, Zemanick ET. Sputum biomarkers of inflammation and lung function decline in children with cystic fibrosis. *Am J Respir Crit Care Med*. 2012;186(9):857-865.
27. Chalmers JD, Moffitt KL, Suarez-Cuartin G, et al. Neutrophil elastase activity is associated with exacerbations and lung function decline in bronchiectasis. *Am J Respir Crit Care Med*. 2017;195(10):1384-1393.
28. Chalmers JD, Goeminne P, Aliberti S, et al. The bronchiectasis severity index. An international derivation and validation study. *Am J Respir Crit Care Med*. 2014;189(5):576-585.
29. Martinez-Garcia MA, de Gracia J, Vendrell Relat M, et al. Multidimensional approach to non-cystic fibrosis bronchiectasis: the FACED score. *Eur Respir J*. 2014;43(5):1357-1367.
30. McDonnell MJ, Aliberti S, Goeminne PC, et al. Multidimensional severity assessment in bronchiectasis: an analysis of seven European cohorts. *Thorax*. 2016;71(12):1110-1118.
31. Olivier KN, Weber DJ, Wallace RJ Jr, et al. Nontuberculous mycobacteria. I: Multicenter prevalence study in cystic fibrosis. *Am J Respir Crit Care Med*. 2003;167(6):828-834.
32. Food and Drug Administration. Issues in the design of clinical trials of antibacterial drugs for the treatment of non-cystic fibrosis

bronchiectasis; public workshop. https://www.federalregister.gov/documents/2012/08/16/2012-20106/issues-in-the-design-of-clinical-trials-of-antibacterial-drugs-for-the-treatment-of-non-cystic. Accessed June 11, 2018.

33. Center for Drug Evaluation and Research (CDER), US Food and Drug Administration (FDA). The voice of the patient. http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM496941.pdf. Accessed June 11, 2018.

34. Quittner AL, Marciel KK, Salathe MA, et al. A preliminary quality of life questionnaire-bronchiectasis: a patient-reported outcome measure for bronchiectasis. *Chest*. 2014;146(2):437-448.

35. Quittner AL, Madan A, Saez-Flores E. Development of a quality of life measure for nontuberculous mycobacteria (NTM). Proceedings from the ERS International Congress; September 26-30, 2015; Amsterdam, The Netherlands: 275.