



Early View

Review

Assessment of factors and interventions towards therapeutic adherence among persons with non-cystic fibrosis bronchiectasis

Christina S. Thornton, Ranjani Somayaji, Rachel K Lim

Please cite this article as: Thornton CS, Somayaji R, Lim RK. Assessment of factors and interventions towards therapeutic adherence among persons with non-cystic fibrosis bronchiectasis. *ERJ Open Res* 2022; in press (<https://doi.org/10.1183/23120541.00340-2022>).

This manuscript has recently been accepted for publication in the *ERJ Open Research*. It is published here in its accepted form prior to copyediting and typesetting by our production team. After these production processes are complete and the authors have approved the resulting proofs, the article will move to the latest issue of the ERJOR online.

Copyright ©The authors 2022. This version is distributed under the terms of the Creative Commons Attribution Non-Commercial Licence 4.0. For commercial reproduction rights and permissions contact permissions@ersnet.org

**Assessment of Factors and Interventions Towards Therapeutic Adherence Among Persons
with Non-Cystic Fibrosis Bronchiectasis**

Christina S. Thornton MD PhD^{1,2*}, Ranjani Somayaji MD MPH^{2,3,4} and Rachel K Lim MD
MPH¹

¹Division of Respiriology, Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada.

²Department of Microbiology, Immunology, and Infectious Diseases, University of Calgary, Calgary, AB, Canada

³Division of Infectious Diseases, Department of Medicine, Cumming School of Medicine, University of Calgary, Calgary, AB, Canada.

⁴Department of Community Health Sciences, University of Calgary, Calgary, Canada

*Corresponding Author
Health Sciences Centre, Foothills Medical Centre
University of Calgary
3330 Hospital Drive NW
Calgary, AB, Canada, T2N 4N1
christina.thornton@albertahealthservices.ca

Summary: Character count with spaces: 256.

Adherence to therapy is a complex interplay of multiple factors with significant impact on clinical outcomes. Here we present the first comprehensive review evaluating the evidence and challenges surrounding such adherence interventions in bronchiectasis.

Abstract Count: 160.

Manuscript Count: 2815.

Abstract:

Non-cystic fibrosis bronchiectasis (NCFB) is a highly prevalent chronic respiratory disease with substantial burden to both patients and health care systems. Persons with NCFB (pwNCFB) are often given complex acute and chronic treatment regimens consisting of medications, airway clearance techniques and exercise. Accordingly, the high burden in NCFB has contributed to lower therapy adherence with estimates of 53% to medications, 41% to airway clearance and only 16% to all prescribed therapy. Consequent clinical outcomes from lower adherence include reduced quality of life, accelerated lung function decline and recurrent pulmonary exacerbations. In this narrative review, we explore the impact of multifactorial mechanisms underpinning adherence in NCFB and evaluate the available evidence towards interventions to improve uptake of therapy as demonstrated in other chronic respiratory diseases. A holistic approach, starting with a careful review of patient adherence at regular intervals, may increase the success of multidimensional therapeutic interventions in pwNCFB, but robust ongoing studies are an area of need in this population.

Introduction:

Non-cystic fibrosis bronchiectasis (NCFB), characterized by cycles of inflammation and chronic infection, was once considered the ‘most neglected disease’ in all of respiratory medicine [1]. Over the last decade, prevalence of NCFB has increased by 40% and is now estimated to be up to 566 per 100,000 people [2], making it the third most common chronic airways disease [3]. Despite this rise, NCFB remains relatively neglected, undertreated and underserved in part due to heterogeneity of underlying etiologies and diverse clinical presentations [4, 5]. Consequently, the burden and mortality of NCFB is high with estimated annual healthcare costs of US\$630 million [6] and hospital admissions ranging from 2 to 6 per 100,000 [7].

The World Health Organization (WHO) has suggested that medication adherence in chronic disease is at best 50% and has not changed substantially over the last half century [8]. Non-adherence limits the ability to maximize full therapeutic efficacy and may result in adverse clinical outcomes and higher healthcare costs [9]. In a cohort of NCFB patients, only 16% were adherent to all prescribed treatments (as defined by an >80% threshold) with non-adherence associated with increased pulmonary exacerbation (PE_x) frequency [10]. Adherence behavior is complex and involves patient, clinician, and healthcare system factors [9]. Tailored interventions designed to improve adherence across multiple chronic diseases have been modest across short and long-term outcomes [10]. Moreover, given the complexity of NCFB medications, dosing regimens and patient factors—there is no simple ‘one-size-fits-all’ approach.

Herein, we will describe the available evidence and ongoing challenges around adherence interventions in NCFB. Using the terms “bronchiectasis,” “non-cystic fibrosis bronchiectasis,”

“adherence” and “interventions,” a search was carried with the following databases used: Pubmed, Embase, Annual Reviews, Biomedical Central Journals Complete, Cochrane database of systematic reviews, Cochrane database, and JAMA Network. Only articles written in English were included in this narrative review.

Current Approach to Bronchiectasis Management:

Persons with NCFB (pwNCFB) are given a complex regimen of medications, airway clearance techniques and exercise with the primary goals to improve daily symptoms and reduce both number and severity of PEx [3]. While not fully explored in NCFB, studies completed in the pre-modulator era of cystic fibrosis (CF) identified an average of seven daily therapies and a mean reported time spent on treatment of 108 minutes [11]. Moreover, those with secondary causes of bronchiectasis have additional management challenges directed at their underlying pathophysiology. Further complicating optimal treatment regimens is the absence of high-quality evidence of their effectiveness [12]. To date, there are no therapeutic options approved by regulatory agencies to attenuate disease progression [13] and treatment regimens are frequently used ‘off-label’. While increasing development of therapeutics in NCFB is emerging with promising applications, the potential impact(s) on future adherence remains unknown [1].

Airway clearance and muco-active therapies, considered as standard of care and recommended for all patients, are the backbone of treatment to minimize airway damage, improve lung function and quality of life [12]. Despite the aforementioned benefits, these treatments are amongst the most burdensome and time consuming to patients with associated high expense. Compounding the time requirement towards therapy, proper maintenance of airway clearance

devices is critical to attenuate risk of infection [14]. As disease progression occurs, additional airway clearance interventions may need to be included [14].

Benefits of inhaled antibiotics in NCFB include attenuation or cessation of recurrent cycles of infection that normally perpetuate lung damage. In those with frequent exacerbations and/or chronic *P. aeruginosa* infection, recommendations are to commence inhaled antibiotic therapy [15]. Notably, this population were those identified as having worse clinical outcomes including increased frequency and shorter duration to subsequent PEx when taking their therapies infrequently [10]. Other pharmacological measures to manage NCFB include inhaled short- and long-acting bronchodilators. While these may be effective in those with documented airway obstruction [16], inhaler adherence is often suboptimal due to co-existing complex therapeutic regimens, limited patient insight on disease and high associated costs [17]. Finally, anti-inflammatory therapy with macrolides has arguably the most robust evidence with several randomized placebo-controlled trials [18-20] demonstrating lower frequency of PEx, although downsides include an increased pill burden and exposure to potential adverse effects.

Consequences of Suboptimal Adherence and Associated Disease Outcomes:

Defining and outlining patient expectations are critical to evaluate impact of treatment (Table 1) with current evidence suggesting adherence to maintenance therapy for NCFB is poor due to multifactorial reasons (Figure 1). McCullough *et al* followed a cohort of 75 patients for one-year using prescription data and strikingly found only 16% were adherent to all treatments [10]. When broken down, about half of the subjects were adherent to their inhaled antibiotics while 41% were adherent to airway clearance techniques. Guan W *et al.* described similar findings with only

40% of patients reporting continuous use of maintenance therapy [21]. A recent systematic review identified that adherence rates were approximately 51% to optimal chest physiotherapy [22].

Suboptimal adherence to treatment can lead to negative health consequences, including increased pulmonary exacerbations, worse symptom control, and lower quality of life. In an observational study done over a one-year period, non-adherence was independently associated with increased PEx compared to patients who were adherent to their inhaled antibiotics [10]. Moreover, non-adherence to chest physiotherapy was associated with lower health-related quality of life. A randomized clinical trial of nebulized colistin administered by a novel delivery device (I-neb) that records the number of administered doses was unable to demonstrate a benefit compared to placebo; however, this was driven by increased PEx among nonadherent participants in the intervention group [23]. In a subgroup analysis of those with greater than 80% adherence, the median time to first PEx was significantly prolonged in the nebulized colistin group compared to the placebo group (168 vs. 103 days, $P=.038$). Moreover, the adherent cohort experienced fewer PEx and improved quality of life scores compared to the placebo group. Although robust evidence for airway clearance techniques is modest, they are frequently recommended to help keep the airways clear of mucus. In a systematic review of the impact of chest physiotherapy adherence on health outcomes among those with CF related bronchiectasis, results were mixed but suggested an association with improved lung function and reduced hospitalizations [22].

Adherence: is More Always Better?

The current development of novel therapeutics, along with leveraging potential of those already in existence, has immense potential to fill current gaps in the management of pwNCFB.

However, further addition(s) to already complex medical regimens come at the cost of increasing treatment burden to patients. As chronic diseases such as NCFB grow in prevalence, healthcare providers have redirected focus from treatment of acute illness with intense but relatively brief regimens to management of patients living with disease [24]. Moreover, given NCFB rarely occurs in isolation, multimorbid conditions further add to complexity of therapeutics and compound treatment burden. The degree of burden felt by patients is influenced by a number of factors including older age, illness duration and severity and multiple comorbidities [25]; many of which describe a large proportion of pwNCFB. Moreover, patient perception of burden is dynamic and can change throughout the course of their illness, depending on severity and impact.

While suboptimal adherence is associated with negative consequences as outlined in the prior section, healthcare providers must be cognisant of the precarious balance of adherence and treatment burden. One such approach may entail an approach of ‘minimally disruptive medicine’, first introduced by May, *et al* [26] suggested clinicians may help reduce treatment burden, and consequently attenuate the vicious cycle of suboptimal adherence, by tailoring treatment regimens to the realities of the daily lives of patients by four pillars: I) establishing the weight of burden through reliable tools, such as patient reported outcomes, to identify overburdened patients and those with capacity problems; II) encouragement of coordination in clinical practice to manage complexity and comorbidity as the goal, as opposed to specific outcomes; III) acknowledgement of comorbidity in clinical evidence through guidelines or clinical trials that include multimorbid patients; and IV) prioritization from the patient perspective as part of shared decision making. While this has been largely unexplored in NCFB currently, delineating the balance of treatment burden with adherence will be a priority for both healthcare providers and patients in the future.

Interventions to Increase Adherence in Bronchiectasis:

In evaluation of evidence-based interventions to improve adherence in NCFB, prior systematic reviews have failed to identify robust published interventions [27]. However, alternative avenues including patient centered programs aimed at improving self-efficacy in bronchiectasis management have been explored. Lavery *et al.* performed a proof-of-concept randomized trial of an expert patient program for patients recruited from a specialty bronchiectasis clinic [28]. A small signal of benefit was most evident immediately post-intervention but did not demonstrate any statistically significant differences in self-efficacy or quality of life, attributed in part due to the small study cohort. A bronchiectasis empowerment tool that included an action plan and education sessions for patients was evaluated in a randomized controlled trial of 127 patients in the United Kingdom; however, at the primary endpoint of one-year there was no significant difference in self-efficacy scores [29]. Both of these trials reported positive patient reported feedback, suggesting larger studies of self-management tools are warranted.

The Change AdhereNce to treatment in BronchiEctasis, CAN-BE, is a proposed approach to developing and delivering an adherence intervention in bronchiectasis [30]. Based on interviews with patients and health care professionals, twelve behaviour change techniques were recommended to consider in an individualized intervention. These included components such as monitoring, action planning, graded tasks, education regarding the behaviour and outcome, and social support. Multifaceted interventions, in contrast to those solely based on providing disease and treatment education, are expected to have more successful outcomes and should be considered in NCFB.

Lessons Learned from Other Chronic Lung Diseases:

While robust evidence is currently lacking in NCFB, other chronic respiratory diseases including asthma, chronic obstructive pulmonary disease (COPD) and CF have systematically evaluated interventions to improve adherence. We believe these lessons and ideas provide a framework that may be applied towards pwNCFB and an area of opportunity towards future studies (Table 2).

Care Coordination:

Care coordination has been shown to improve the quality of care for COPD, asthma and neuromuscular patients with the core pillar of ‘patient-centered systems where they are informed about their disease and therapeutic plans, so they may become the main protagonist in clinical care decisions’, thereby promoting greater therapy adherence [31]. The use of interstitial lung disease (ILD) specialist nurses in the care of these patients has been critical for disease education, surveillance of drug side-effects and discussion of care options [32]. Indeed, the introduction of ILD specialist nurses has been shown to increase treatment adherence with reduction in need for dose reduction and/or discontinuation of antifibrotic agents [33, 34]. Outreach programs, whether provided in-home or in a pharmacy, have improved medication adherence among patients with COPD but it is unclear if this benefit persists after regular contact is discontinued [35].

Self-management and education:

The use of standard education compared to an individualized four-step problem-solving technique with identifying specific barriers to adherence, brainstorming solutions with the patient, appraising the options together to choose the best solution, and then subsequent amendment of the

intervention based on its impact was used on a cohort of adult moderate-to-severe asthma patients [36]. While adherence did decline across both groups, measures of asthma control including quality of life, asthma-control questionnaire and ppFEV₁ improved in the intervention arm compared to the usual care group. Action plans based on symptom and peak flow monitoring have been used for proactive self-management in asthma. A study of 400 asthmatic adults found the implementation of an action plan was associated with greater adherence and fewer severe exacerbations at 6 months [37]. Such self-management plans for COPD have led to reduced hospital admissions (OR 0.69, 95% confidence interval 0.49, 0.97) and emergency department visits (OR 0.55, 95% CI 0.38, 0.78) and improved quality of life scores [38]. Whether a bronchiectasis action management plan can improve clinical outcomes is unknown, but it seems feasible that such a tool could lead to better self-recognition of signs and symptoms and improve patient empowerment.

Reminders:

The use of inhaler reminders provides a promising avenue to improve adherence, however real-world studies have demonstrated mixed benefit. Charles, *et al* utilized reminder devices attached to an inhaler to provide both audio and visual reminders at predesigned times in a cohort of asthmatic patients with significantly ($P < .0001$) higher adherence at 24 weeks (93%) compared to standard care (74%) [39]. A study of moderate to severe asthma subjects investigated the change in inhaled corticosteroid/long-acting β -agonist adherence by use of an inhaler reminder with feedback, family physician-delivered personalized discussions and usual care. While after 6 months adherence was again significantly higher in the reminder group, there was no significant difference between groups in asthma control [40]. Reminders have also been explored for

improving adherence to tuberculosis treatment in endemic countries. A higher frequency of treatment success was shown in a medication event reminder group (MERM) compared to the traditional directly observed group in one study conducted in Peru [41].

Digital Technology and Electronic Monitoring Devices (EMDs):

Digital technology has exponentially increased in demand given the COVID-19 pandemic with global healthcare challenges, forcing innovative strategies to be implemented. In COPD, the use of digital technology and home monitoring reduced the use of emergency care and unplanned hospital admissions/readmissions [42, 43]. As with the other interventions described thus far, while EMDs have shown improved adherence, clinical efficacy is less clear [44]. In an asthmatic study using digital audio devices to monitor inhaled therapies, adherence based on the dose counter was 84% but effective adherence (defined as area under the concentration–time curve) was only 62%, suggesting doses were ineffective and/or not taken regularly [45]. The use of technology to monitor adherence in airway clearance techniques has been used mainly in research settings, but a recent pragmatic study evaluated this using oscillating positive expiratory pressure (PEP) devices with a pressure transducer in a small cohort of 10 adults with CF [46]. Similar applications have been applied to nebulized aerosol delivery systems in adult CF patient cohorts with overall higher adherence during study enrollment but unknown long-term sustained effects [47]. Recently, a multi-centre trial, *conneCT CF*, aiming to evaluate use of a self-management app, video-conferencing and telephone coaching on adherence to treatment, lung function, and PEx in CF has been proposed with results currently pending, but may translate to applicability in NCFB patients [48].

Current Gaps and Future Directions:

Suboptimal adherence has clearly been associated with adverse health outcomes in NCFB including shorter time to [23] and more frequent PEx [10]. Despite the postulated benefits of adherence, several studies across other chronic lung diseases have failed to consistently demonstrate subsequent improvements in morbidity, mortality, healthcare burden, quality of life and/or patient satisfaction [8]. Discordance of improved adherence and clinical outcomes may be in part due to bias from the Hawthorne effect (i.e., where individuals modify and/or improve behaviour in response to heightened awareness from enrollment in a trial) and may explain observations in several studies of improved adherence in both control and intervention arms [8].

High-quality randomized control trials to evaluate adherence interventions are critical to the optimal management of NCFB but are lacking due to multifactorial reasons including absence of dedicated clinical funding, lack of specialist staff for bronchiectasis clinics, perceived low priority of adherence management by clinicians and limited confidence by care providers to challenge patient adherence patterns [30]. Other important factors include heterogeneity of the underlying disease(s) contributing to bronchiectasis and subsequent difficulty in achieving statistical power in sub-group analysis during clinical study design [27]. These hurdles require involvement of multiple centres through dedicated patient registries to increase enrollment as well as standardization of protocols. Evaluation of adherence to therapy underpins the success of larger research efforts to identify novel and effective treatments. New treatments are emerging, such as brensocatib, a novel anti-inflammatory therapy targeting neutrophilic inflammation, recently shown to have good efficacy in a phase 2 trial [49]. As such, robust measures of adherence in the

era of new developments in therapy will become even more of a priority to all key stakeholders involved (Figure 1).

Conclusions:

NCFB is one of the few fields in pulmonary medicine that has had such rapid development and heightened awareness as has been observed in the last decade [1]. Precision medicine approaches to target individual patient needs are currently underway to improve clinical outcomes while minimizing unnecessary side effects and burden. Healthcare providers should strive to develop adherence-promotion strategies in a similar individualized approach that account for the shared barriers across NCFB populations. As we have learned with other chronic respiratory diseases, multifaceted interventions will almost certainly be more effective at enhancing therapy adherence in NCFB. Whilst these adherence interventions are appealing and intuitively beneficial, further dedicated studies evaluating the impact of these interventions on clinical outcomes are needed to support the applicability to daily practice in the care of pwNCFB.

Table 1: Adherence Terminology and Nomenclature

Term	Description^a
Adherence	Process by which patients take their therapy (i.e., medications) as prescribed.
<ul style="list-style-type: none"> • Initiation • Implementation 	<ul style="list-style-type: none"> Moment at which the patient takes the first dose of a prescribed therapy and/or medication. Extent to which a patient’s actual dosing corresponds to the prescribed dosing regimen from initiation until the last dose taken.
<ul style="list-style-type: none"> • Discontinuation • Persistence 	<ul style="list-style-type: none"> Being the end of therapy, when the next dose to be taken is omitted and no more doses are taken thereafter. Length of time between initiation and the last dose which immediately precedes discontinuation.
Compliance	Extent to which patients follow healthcare provider directions.
Patient Expectations	Anticipation or belief of perceived benefit of therapy, related to adherence (i.e., patients may adhere well because of strong expectations for treatment success).
Dimensions of Adherence	Factors related to maintenance of adherence as outlined by the World Health Organization (WHO).
<ul style="list-style-type: none"> • Patient • Healthcare System • Condition • Social and Economic • Therapy 	<ul style="list-style-type: none"> Age, socioeconomic group, motivation, knowledge of disease, perceived risks of disease, perceived benefit of treatment. Patient-provider relationship, care continuity, wait-times. Symptom severity, concurrent depression. Cultural beliefs, language barriers, community support, therapy costs. Complexity of medical regimen, duration of therapy, actual or perceived side effects.

^aAdapted from references [30, 50, 51]

Table 2: Summary of Adherence Interventions Used in Chronic Lung Diseases

Intervention	Definition	Advantages	Disadvantages
Care Coordination	Proactive approach to bring together care providers to meet the needs of patients and ensure they receive integrated person-focused care across various settings.	<ul style="list-style-type: none"> • Efficient and specialized, removes burden from individual healthcare provider. 	<ul style="list-style-type: none"> • Feasibility and scalability may be barrier for many practices and healthcare systems.
Self-Management and Education	Training with feedback to facilitate problem solving, decision making and action planning which in turn propagate confidence in health self-management.	<ul style="list-style-type: none"> • Simple, inexpensive. • Promotes patient engagement and empowerment. 	<ul style="list-style-type: none"> • Time consuming. • Difficult to measure outcomes. • Requires patient buy-in.
Reminders	Communication to the patient with reminder notice (i.e., pharmacist calling patient when a prescription has not been filled).	<ul style="list-style-type: none"> • Simple, inexpensive. • Accurate. 	<ul style="list-style-type: none"> • Time consuming. • Does not measure consumption (i.e., refilling at another pharmacy). • Logistical difficulties (i.e., accessing patient records).
Electronic Medication and Device Monitors (EMDs)	Considered the gold standard for adherence assessment. Device with the ability to provide date, time and treatment duration across several therapeutics (i.e., tablets and aerosol inhalers).	<ul style="list-style-type: none"> • Provides adherence measures not only in real time but also with a longitudinal perspective. • Ability to send text message to a patient's mobile phone if the dispenser device has not been opened and can notify others including the health care worker if doses have been completely missed. • Results are easily identified, tracks pattern of taking medication. 	<ul style="list-style-type: none"> • Connectivity problems. • Expensive. • Reminders most effective when personal and interactive. • Pragmatic concerns of data storage and who/how it may be acted upon. • Expensive, requires return visits and downloading data from medication vials.
Digital Technology	Use of alternative devices to obtain data (i.e., home spirometry).	<ul style="list-style-type: none"> • Ability for physicians to intervene earlier for therapy adjustment. • Ease of use with ability to send text messaging and reminders to patients. 	<ul style="list-style-type: none"> • Connectivity problems. • Expensive.

Figure Legends

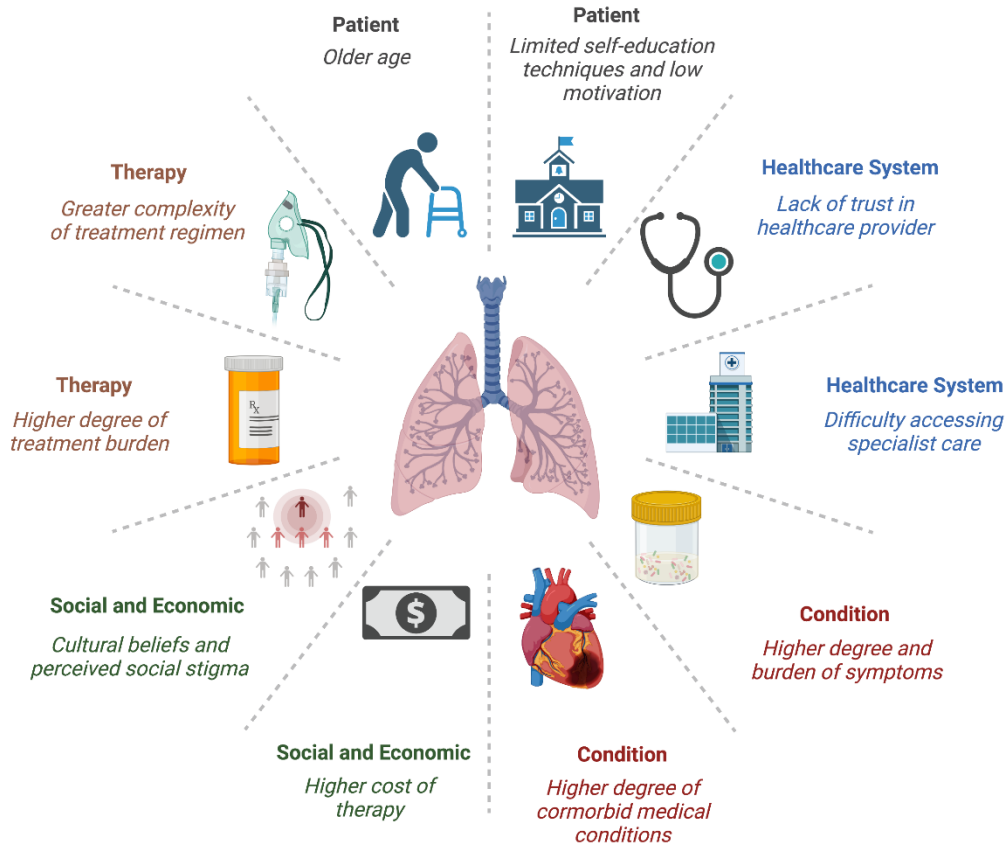


Figure 1: *Factors associated with adherence in non-cystic fibrosis bronchiectasis (NCFB).*

Adapted from study by McCullough, *et al* [52]. Figure created with Biorender (www.biorender.com).

Author Contributions:

CST, RS and RLK all conceptualized the project and wrote the manuscript. All the authors have read and approved the final version of the manuscript.

Conflict of Interest:

There are no conflicts of interests for any authors in regard to this study.

References:

1. Chalmers JD. Bronchiectasis from 2012 to 2022. *Clin Chest Med.* 2022;43(1):1-6; doi: 10.1016/j.ccm.2021.12.001.
2. Quint JK, Millett ER, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *Eur Respir J.* 2016;47(1):186-93; doi: 10.1183/13993003.01033-2015.
3. Cohen R, Shteinberg M. Diagnosis and evaluation of bronchiectasis. *Clin Chest Med.* 2022;43(1):7-22; doi: 10.1016/j.ccm.2021.11.001.
4. Prentice BJ, Wales S, Doumit M, Owens L, Widger J. Children with bronchiectasis have poorer lung function than those with cystic fibrosis and do not receive the same standard of care. *Pediatr Pulmonol.* 2019;54(12):1921-6; doi: 10.1002/ppul.24491.
5. Chalmers JD. Bronchiectasis: Advances in Diagnosis and Management. *Clin Chest Med.* 2022;43(1):xiii; doi: 10.1016/j.ccm.2022.01.001.
6. Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and economic burden of bronchiectasis. *Clinical Pulmonary Medicine.* 2005;12(4):205-9; doi: 10.1097/01.cpm.0000171422.98696.ed.
7. Gibson GJ, Loddenkemper R, Lundback B, Sibille Y. Respiratory health and disease in Europe: the new European Lung White Book. *Eur Respir J.* 2013;42(3):559-63; doi: 10.1183/09031936.00105513.
8. d'Ancona G, Weinman J. Improving adherence in chronic airways disease: are we doing it wrongly? *Breathe (Sheff).* 2021;17(2):210022; doi: 10.1183/20734735.0022-2021.
9. Kini V, Ho PM. Interventions to improve medication adherence: A review. *JAMA.* 2018;320(23):2461-73; doi: 10.1001/jama.2018.19271.
10. 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; doi: 10.1186/1471-2466-14-107.

11. Sawicki GS, Sellers DE, Robinson WM. High treatment burden in adults with cystic fibrosis: challenges to disease self-management. *J Cyst Fibros*. 2009;8(2):91-6; doi: 10.1016/j.jcf.2008.09.007.
12. O'Donnell AE. Medical management of bronchiectasis. *J Thorac Dis*. 2018;10(Suppl 28):S3428-S35; doi: 10.21037/jtd.2018.09.39.
13. Amaro R, Perea L, Sibila O. Future directions in bronchiectasis research. *Clin Chest Med*. 2022;43(1):179-87; doi: 10.1016/j.ccm.2021.12.005.
14. O'Donnell AE. Airway clearance and mucoactive therapies in bronchiectasis. *Clin Chest Med*. 2022;43(1):157-63; doi: 10.1016/j.ccm.2021.12.004.
15. Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn JS, Floto RA, et al. British Thoracic Society guideline for bronchiectasis in adults. *BMJ Open Respir Res*. 2018;5(1):e000348; doi: 10.1136/bmjresp-2018-000348.
16. Franco F, Sheikh A, Greenstone M. Short acting beta2-agonists for bronchiectasis. *Cochrane Database of Systematic Reviews*. 2003;(1); doi: 10.1002/14651858.CD003572.
17. Jardim JR, Nascimento OA. The importance of inhaler adherence to prevent COPD exacerbations. *Med Sci (Basel)*. 2019;7(4); doi: 10.3390/medsci7040054.
18. Wong C, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. *The Lancet*. 2012;380(9842):660-7; doi: [https://doi.org/10.1016/S0140-6736\(12\)60953-2](https://doi.org/10.1016/S0140-6736(12)60953-2).
19. Altenburg J, de Graaff CS, Stienstra Y, Sloos JH, van Haren EHJ, Koppers RJH, 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):1251-9; doi: 10.1001/jama.2013.1937.
20. Serisier DJ, Martin ML, McGuckin MA, Lourie R, Chen AC, Brain B, 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):1260-7; doi: 10.1001/jama.2013.2290.
21. Guan WJ, Huang Y, Chen CL, Chen RC, Zhong NS. Macrolides, mucoactive drugs and adherence for the management of bronchiectasis. *Eur Respir J*. 2018;51(1); doi: 10.1183/13993003.01987-2017.

22. Alyssa Yue Hui Low JST, Rethinam Ganesan, Jaclyn Tan, Albert Yick Hou Lim. Systematic review on adherence, barriers to treatment and impact of airway clearance in bronchiectasis. *Archives of Clinical and Biomedical Research*. 2020;4:481-97.
23. 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(8):975-82; doi: 10.1164/rccm.201312-2208OC.
24. Sav A, Salehi A, Mair FS, McMillan SS. Measuring the burden of treatment for chronic disease: implications of a scoping review of the literature. *BMC Med Res Methodol*. 2017;17(1):140; doi: 10.1186/s12874-017-0411-8.
25. Sav A, King MA, Whitty JA, Kendall E, McMillan SS, Kelly F, et al. Burden of treatment for chronic illness: a concept analysis and review of the literature. *Health Expect*. 2015;18(3):312-24; doi: 10.1111/hex.12046.
26. May C, Montori VM, Mair FS. We need minimally disruptive medicine. *BMJ*. 2009;339:b2803; doi: 10.1136/bmj.b2803.
27. McCullough A, Thomas ET, Ryan C, Bradley JM, O'Neill B, Elborn S, et al. Interventions for enhancing adherence to treatment in adults with bronchiectasis. *Cochrane Database Syst Rev*. 2015;(11):CD011023; doi: 10.1002/14651858.CD011023.pub2.
28. Lavery KA, O'Neill B, Parker M, Elborn JS, Bradley JM. Expert patient self-management program versus usual care in bronchiectasis: a randomized controlled trial. *Arch Phys Med Rehabil*. 2011;92(8):1194-201; doi: 10.1016/j.apmr.2011.03.012.
29. Brockwell C, Stockl A, Clark A, Barton G, Pasteur M, Fleetcroft R, et al. Randomised controlled trial of the effect, cost and acceptability of a bronchiectasis self-management intervention. *Chronic Respiratory Disease*. 2020;17:1479973120948077; doi: 10.1177/1479973120948077.
30. McCullough AR, Ryan C, O'Neill B, Bradley JM, Elborn JS, Hughes CM. Defining the content and delivery of an intervention to Change AdhereNce to treatment in BronchiEctasis (CAN-BE): a qualitative approach incorporating the Theoretical Domains Framework, behavioural change techniques and stakeholder expert panels. *BMC Health Serv Res*. 2015;15:342; doi: 10.1186/s12913-015-1004-z.

31. Pierucci P, Santomasi C, Ambrosino N, Portacci A, Diaferia F, Hansen K, et al. Patient's treatment burden related to care coordination in the field of respiratory diseases. *Breathe (Sheff)*. 2021;17(1):210006; doi: 10.1183/20734735.0006-2021.
32. Shaw J, Marshall T, Morris H, Hayton C, Chaudhuri N. Idiopathic pulmonary fibrosis: a holistic approach to disease management in the antifibrotic age. *J Thorac Dis*. 2017;9(11):4700-7; doi: 10.21037/jtd.2017.10.111.
33. Chaudhuri N, Duck A, Frank R, Holme J, Leonard C. Real world experiences: pirfenidone is well tolerated in patients with idiopathic pulmonary fibrosis. *Respir Med*. 2014;108(1):224-6; doi: 10.1016/j.rmed.2013.11.005.
34. Moran Mendoza O, Aldhaferi S, Mccarthy L. Impact of an interstitial lung diseases Nurse on the compliance to anti-fibrotic drugs in patients with Idiopathic Pulmonary Fibrosis. *European Respiratory Journal*. 2018;52(suppl 62):PA2952; doi: 10.1183/13993003.congress-2018.PA2952.
35. Marron E, Patton D, O'Connor T, Moore Z, Murray B, Nugent LE. What is the impact of outreach services on medication adherence for COPD patients? A systematic review. *COPD*. 2020;17(6):732-41; doi: 10.1080/15412555.2020.1833852.
36. Apter AJ, Wang X, Bogen DK, Rand CS, McElligott S, Polsky D, et al. Problem solving to improve adherence and asthma outcomes in urban adults with moderate or severe asthma: a randomized controlled trial. *J Allergy Clin Immunol*. 2011;128(3):516-23 e1-5; doi: 10.1016/j.jaci.2011.05.010.
37. Farag H, Abd El-Wahab EW, El-Nimr NA, Saad El-Din HA. Asthma action plan for proactive bronchial asthma self-management in adults: a randomized controlled trial. *Int Health*. 2018;10(6):502-16; doi: 10.1093/inthealth/ihy050.
38. Lenferink A, Brusse-Keizer M, van der Valk PD, Frith PA, Zwerink M, Monninkhof EM, et al. Self-management interventions including action plans for exacerbations versus usual care in patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2017;8:CD011682; doi: 10.1002/14651858.CD011682.pub2.
39. Charles T, Quinn D, Weatherall M, Aldington S, Beasley R, Holt S. An audiovisual reminder function improves adherence with inhaled corticosteroid therapy in asthma. *J Allergy Clin Immunol*. 2007;119(4):811-6; doi: 10.1016/j.jaci.2006.11.700.

40. Foster JM, Usherwood T, Smith L, Sawyer SM, Xuan W, Rand CS, et al. Inhaler reminders improve adherence with controller treatment in primary care patients with asthma. *J Allergy Clin Immunol*. 2014;134(6):1260-8 e3; doi: 10.1016/j.jaci.2014.05.041.
41. Acosta J, Flores P, Alarcon M, Grande-Ortiz M, Moreno-Exebio L, Puyen ZM. A randomised controlled trial to evaluate a medication monitoring system for TB treatment. *Int J Tuberc Lung Dis*. 2022;26(1):44-9; doi: 10.5588/ijtld.21.0373.
42. Casas A, Troosters T, Garcia-Aymerich J, Roca J, Hernandez C, Alonso A, et al. Integrated care prevents hospitalisations for exacerbations in COPD patients. *Eur Respir J*. 2006;28(1):123-30; doi: 10.1183/09031936.06.00063205.
43. Hernandez C, Casas A, Escarrabill J, Alonso J, Puig-Junoy J, Farrero E, et al. Home hospitalisation of exacerbated chronic obstructive pulmonary disease patients. *Eur Respir J*. 2003;21(1):58-67; doi: 10.1183/09031936.03.00015603.
44. Dixon E, Puckey M, Collins N, Marsh G, Pabary R. Striving for perfection, accepting the reality: A reflection on adherence to airway clearance and inhalation therapy for paediatric patients with chronic suppurative lung disease. *Paediatr Respir Rev*. 2020;34:46-52; doi: 10.1016/j.prrv.2019.04.002.
45. Sulaiman I, Seheult J, MacHale E, Boland F, O'Dwyer SM, Rapcan V, et al. A method to calculate adherence to inhaled therapy that reflects the changes in clinical features of asthma. *Ann Am Thorac Soc*. 2016;13(11):1894-903; doi: 10.1513/AnnalsATS.201603-222OC.
46. Hoo ZH, Daniels T, Bradley JM, Heller B, Rose C, Wildman M. WS14.6 Feasibility study to objectively measure airway clearance technique in cystic fibrosis. *Journal of Cystic Fibrosis*. 2014;13:S30; doi: [https://doi.org/10.1016/S1569-1993\(14\)60093-X](https://doi.org/10.1016/S1569-1993(14)60093-X).
47. Daniels T, Goodacre L, Sutton C, Pollard K, Conway S, Peckham D. Accurate assessment of adherence: self-report and clinician report vs electronic monitoring of nebulizers. *Chest*. 2011;140(2):425-32; doi: <https://doi.org/10.1378/chest.09-3074>.
48. Thee S, Stahl M, Fischer R, Sutharsan S, Ballmann M, Muller A, et al. A multi-centre, randomized, controlled trial on coaching and telemonitoring in patients with cystic fibrosis: conneCT CF. *BMC Pulm Med*. 2021;21(1):131; doi: 10.1186/s12890-021-01500-y.

49. Chalmers JD, Haworth CS, Metersky ML, Loebinger MR, Blasi F, Sibila O, et al. Phase 2 Trial of the DPP-1 inhibitor brensocatic in bronchiectasis. *N Engl J Med*. 2020;383(22):2127-37; doi: 10.1056/NEJMoa2021713.
50. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppert T, et al. A new taxonomy for describing and defining adherence to medications. *Br J Clin Pharmacol*. 2012;73(5):691-705; doi: 10.1111/j.1365-2125.2012.04167.x.
51. Cramer JA, Roy A, Burrell A, Fairchild CJ, Fuldeore MJ, Ollendorf DA, et al. Medication compliance and persistence: terminology and definitions. *Value Health*. 2008;11(1):44-7; doi: 10.1111/j.1524-4733.2007.00213.x.
52. McCullough AR, 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 Expect*. 2015;18(6):2477-88; doi: 10.1111/hex.12217.