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

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Adherence to therapy is a complex interplay of multiple factors with significant impact on clinical outcomes. This is the first comprehensive review evaluating the evidence and challenges surrounding such adherence interventions in bronchiectasis. https://bit.ly/3TcvnqX

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Abstract

Non-cystic fibrosis bronchiectasis (NCFB) is a highly prevalent chronic respiratory disease with substantial burden to both patients and healthcare 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), characterised by cycles of inflammation and chronic infection, was once considered the “most neglected disease” in all of respiratory medicine [1]. Over the last decade, the 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 underserviced, in part due to heterogeneity of underlying aetiologies and diverse clinical presentations [4, 5]. Consequently, the burden and mortality of NCFB is high, with estimated annual healthcare costs of USD 630 million [6] and hospital admissions ranging from 2 to 6 per 100 000 [7].

The World Health Organization 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 maximise 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 a >80% threshold), with non-adherence associated with increased pulmonary exacerbation frequency [10]. Adherence behaviour 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 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 out using 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 pulmonary exacerbations [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 min [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 remain(s) unknown [1].

Airway clearance and mucoactive therapies, considered as standard of care and recommended for all patients, are the backbone of treatment to minimise airway damage, and improve lung function and quality of life [12]. Despite the aforementioned benefits, these treatments are among 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 *Pseudomonas aeruginosa* infection, recommendations are to commence inhaled antibiotic therapy [15]. Notably, this population was identified as having worse clinical outcomes, including increased frequency and shorter duration to subsequent pulmonary exacerbation, 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 coexisting 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 randomised placebo-controlled trials [18–20] demonstrating lower frequency of pulmonary exacerbation, 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.* [10] followed a cohort of 75 patients for 1 year using prescription data and strikingly found only 16% were adherent to all treatments. When broken down, about half of the subjects were adherent to their inhaled antibiotics while 41% were adherent to airway clearance techniques. Guan *et al.* [21] described similar findings, with only 40% of patients reporting continuous use of maintenance therapy. A recent systematic review identified that adherence rates were ∼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 performed over a 1-year period, non-adherence was independently associated with increased pulmonary exacerbations compared with 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 randomised clinical trial of nebulised colistin administered by a novel delivery device (I-neb adaptive aerosol delivery device; Philips Respironics, Chichester, UK) that records the number of administered doses was unable to demonstrate a benefit compared with placebo; however, this was driven by increased pulmonary exacerbations among non-adherent participants in the intervention group [23]. In a subgroup analysis of those with >80% adherence, the median time to first pulmonary exacerbation was significantly

TABLE 1 Adherence terminology and nomenclature

Term	Description[#]
Adherence	Process by which patients take their therapy (*i.e.* medications) as prescribed
Initiation	Moment at which the patient takes the first dose of a prescribed therapy and/or medication
Implementation	Extent to which a patient's actual dosing corresponds to the prescribed dosing regimen from initiation until the last dose taken
Discontinuation	Being the end of therapy, when the next dose to be taken is omitted and no more doses are taken thereafter
Persistence	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
Patient	Age, socioeconomic group, motivation, knowledge of disease, perceived risks of disease, perceived benefit of treatment
Healthcare system	Patient–provider relationship, care continuity, wait times
Condition	Symptom severity, concurrent depression
Social and economic	Cultural beliefs, language barriers, community support, therapy costs
Therapy	Complexity of medical regimen, duration of therapy, actual or perceived side-effects

[#]: adapted from [30, 50, 51].

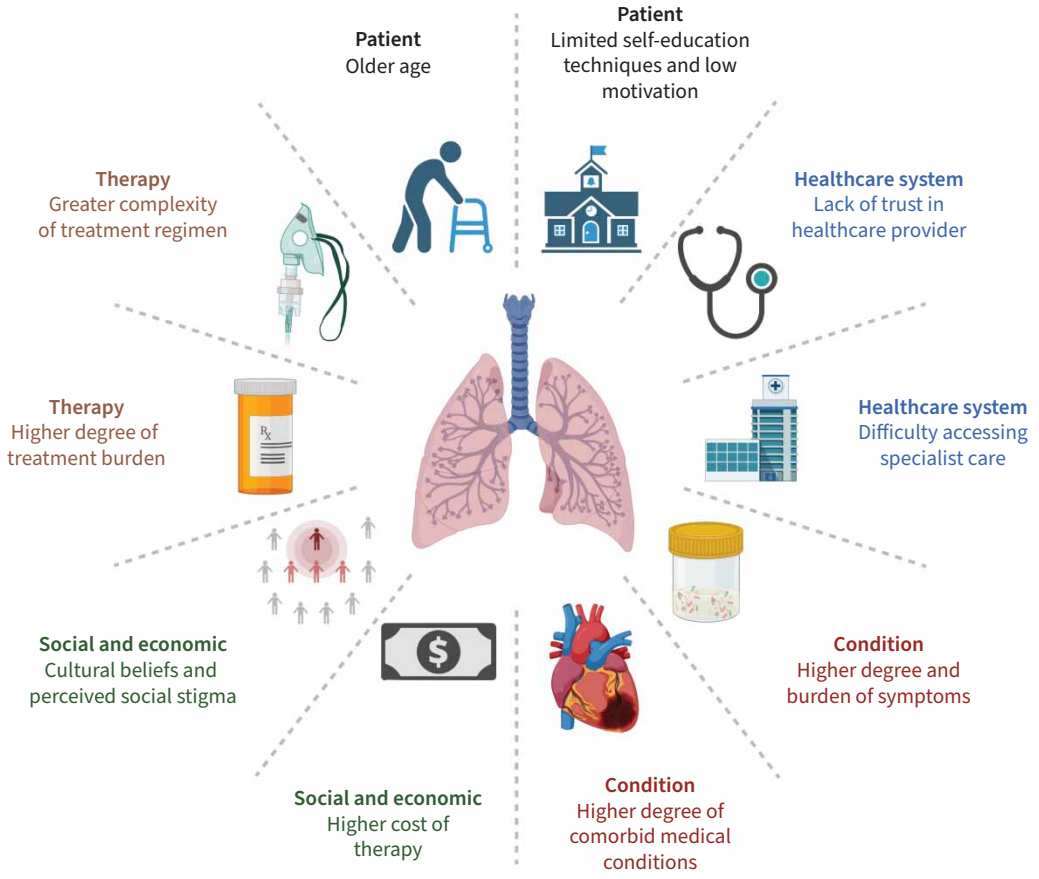

FIGURE 1 Factors associated with adherence in non-cystic fibrosis bronchiectasis. Adapted from study by McCullough *et al.* [52]. Figure partially created with Biorender.com.

prolonged in the nebulised colistin group compared with the placebo group (168 *versus* 103 days; p=0.038). Moreover, the adherent cohort experienced fewer pulmonary exacerbations and improved quality of life scores compared with 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 hospitalisations [22].

Adherence: is more always better?

The current development of novel therapeutics, along with leveraging the 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 the 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 the illness, depending on severity and impact.

While suboptimal adherence is associated with negative consequences as outlined in the previous 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] who 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: 1) establishing the weight of burden through reliable tools, such as patient-reported outcomes, to identify overburdened patients and those with capacity problems; 2) encouraging coordination in clinical practice to manage complexity and comorbidity as the goal, as opposed to specific outcomes; 3) acknowledging comorbidity in clinical evidence through guidelines or clinical trials that include multimorbid patients; and 4) prioritising 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

When evaluating evidence-based interventions to improve adherence in NCFB, prior systematic reviews have failed to identify robust published interventions [27]. However, alternative avenues including patient-centred programmes aimed at improving self-efficacy in bronchiectasis management have been explored. Lavery *et al.* [28] performed a proof-of-concept randomised trial of an expert patient programme for patients recruited from a specialty bronchiectasis clinic. 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 randomised controlled trial of 127 patients in the UK; however, at the primary end-point of 1 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.

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 healthcare professionals, 12 behaviour change techniques were recommended to be considered in an individualised 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, 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).

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	Efficient and specialised, removes burden from individual healthcare provider	Feasibility and scalability may be barriers 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	Simple, inexpensive; promotes patient engagement and empowerment	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)	Simple, inexpensive; accurate	Time consuming; does not measure consumption (*i.e.* refilling at another pharmacy); logistical difficulties (*i.e.* accessing patient records)
Electronic medication and device monitors	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)	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 healthcare worker if doses have been completely missed; results are easily identified; tracks pattern of taking medication	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)	Ability for physicians to intervene earlier for therapy adjustment; ease of use with ability to send text messages and reminders to patients	Connectivity problems; expensive

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-centred 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 a reduction in the need for dose reduction and/or discontinuation of antifibrotic agents [33, 34]. Outreach programmes, 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 with an individualised four-step problem-solving technique, *i.e.* 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 percentage predicted forced expiratory volume in 1 s, improved in the intervention arm compared with 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 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% CI 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.* [39] utilised reminder devices attached to an inhaler to provide both audio and visual reminders at predesignated times in a cohort of asthmatic patients, with significantly ($p<0.0001$) higher adherence at 24 weeks (93%) compared with standard care (74%). 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 personalised 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 compared with the traditional directly observed group in one study conducted in Peru [41].

Digital technology and electronic monitoring devices

Digital technology has exponentially increased in demand given the coronavirus disease 2019 (COVID-19) pandemic and associated 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 digital technology and electronic monitoring devices have shown improved adherence, clinical efficacy is less clear [44]. In an asthma 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 devices with a pressure transducer in a small cohort of 10 adults with CF suggested that self-report overestimated adherence [46]. Similar applications have been applied to nebulised aerosol delivery systems in adult CF patient cohorts with overall higher adherence during study enrolment but unknown long-term sustained effects [47]. Recently, a multicentre trial, conneCT CF, aiming to evaluate use of a self-management app, video-conferencing and telephone coaching on adherence to treatment, lung function and pulmonary exacerbation 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 pulmonary exacerbations [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 enrolment in a trial), and may explain observations in several studies of improved adherence in both control and intervention arms [8].

High-quality randomised 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 subgroup analysis during clinical study design [27]. These hurdles require involvement of multiple centres through dedicated patient registries to increase enrolment as well as standardisation 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 that was 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 minimising unnecessary side-effects and burden. Healthcare providers should strive to develop adherence promotion strategies in a

similar individualised 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. While 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.

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