

# Management of non-cystic fibrosis bronchiectasis

Syba Susan Sunny<sup>1</sup>, John Davison<sup>1</sup> & Anthony De Soyza<sup>\*1,2</sup>



## Practice Points

- Bronchiectasis is a respiratory disease with various causes, such as postinfection injury immunodeficiency and cystic fibrosis, and is characterized by permanently dilated thick-walled large airways. It typically causes symptoms of a persistent productive cough and shortness of breath.
- Non-cystic fibrosis bronchiectasis, often considered an 'orphan disease', is associated with significant morbidity and mortality; recent data suggest it is responsible for more than 11,400 hospital admissions in the UK annually.
- Patients with non-cystic fibrosis bronchiectasis may account for 0.05% of the UK population, yet attract low levels of research interest.
- Current clinical practice does not correlate well with recent national guidelines set out by the British Thoracic Society, reflecting the guidelines' poor evidence base due to a lack of available trial data and probably a desire to individualize treatment to patients as required.
- Novel 'maintenance' therapies currently under investigation in non-cystic fibrosis bronchiectasis include neutrophil elastase inhibitors, inhaled hypertonic saline and adjunct devices to assist mucus mobilization in chest physiotherapy.
- Large-scale clinical trials are also in progress to determine the effectiveness of regular courses of antimicrobials delivered via the nebulized/inhaled route in treating chronic low-grade respiratory tract infection.
- Further commercial interest will be valuable in order to optimize patient care in the future.

<sup>1</sup>Sir William Leech Centre for Lung Research, Adult Bronchiectasis Service, Freeman Hospital, Newcastle upon Tyne, UK

<sup>2</sup>Institute of Cellular Medicine, Newcastle University & Honorary Consultant in Respiratory Medicine, Adult Bronchiectasis Service, Freeman Hospital, Newcastle upon Tyne, UK

\*Author for correspondence: Tel.: +44 191 223 1148; Fax: +44 191 223 1690; anthony.de-soyza@ncl.ac.uk

**SUMMARY** Non-cystic fibrosis bronchiectasis, often considered an ‘orphan disease’, represents a substantial cause of hospital admission and primary care consultations. As yet, the management of this chronic disease has been hampered by an inadequate evidence base. This has led to the occasionally inappropriate extrapolation of research from other chronic respiratory diseases with potentially different disease processes or trajectories, such as cystic fibrosis and chronic obstructive pulmonary disease. Recently, commercial interest in bronchiectasis has increased, raising the possibility of new evidence-based treatment options for the stable phases of the disease. These maintenance therapies include long-term antibiotic therapy and inhaled mucolytic therapies. This article reviews current clinical practice in the routine management of non-cystic fibrosis bronchiectasis and discusses emerging therapeutic options.

Bronchiectasis is a term that denotes a respiratory disease state characterized by abnormally dilated, thick-walled bronchi and bronchioles with evidence of both inflammation and chronic bacterial infections. This pathological state typically manifests itself clinically with a chronic or persistent productive cough, dyspnea and fatigue [1]. The etiology of bronchiectasis is varied and includes cystic fibrosis, postinfection lung injury, primary ciliary dyskinesia, immunodeficiency and allergic bronchopulmonary aspergillosis. Up to 50% of patients with moderately severe chronic obstructive pulmonary disease (COPD) may also show evidence of bronchiectasis [2]. Hence, bronchiectasis can complicate other pre-existing pulmonary diseases. However, for a large number of patients, the cause is unknown – the so-called ‘idiopathic’ bronchiectasis [3–5]. Regardless of etiological origin, bronchiectasis is associated with significant levels of physical and social morbidity and incurs considerable healthcare costs [6].

Although cystic fibrosis (CF)-associated lung disease demonstrates bronchiectasis, CF-related disease is most often viewed as a separate entity from bronchiectasis attributed to other etiologies. This is due to obvious differences in its prognosis, microbiology, epidemiology and underlying pathophysiology (i.e., related to mutation(s) present in the *CFTR* gene in CF). As such, the treatment of CF and the clinical trials data that underpin its management cannot simply be translated to non-cystic fibrosis bronchiectasis (NCFBr) [7]. Herein, we will focus on the routine management of NCFBr.

#### Burden of disease

Bronchiectasis, often considered an ‘orphan disease’, is an increasingly recognized cause

of hospital admissions, primary care consultations and antibiotic prescriptions. Seitz *et al.* reported an annual age-adjusted in-patient admission rate of 16.5 per 100,000 population in the US [6]. In the UK, it has been suggested that primary care physicians may have up to 12 bronchiectasis patients each within an average patient population of 2500 patients [8]. Meanwhile, Healthcare Resource Group data available from the British Thoracic Society (BTS) website noted over 11,490 bronchiectasis admissions in the UK in a 1-year period (2009–2010) [101].

NCFBr is also associated with a considerable level of mortality; a follow-up study of patients in Turkey with a mean age of 61 and without significant coexisting life-limiting illness described a surprisingly low survival rate of 58% at 4 years [9]. However, other more recent follow-up studies describe a variety of more favorable mortality rates, ranging from 7.5 to 29.7% [10–12]. Of these, the study that noted both the highest mortality rate and the longest follow-up period (13 years) attributed the cause of death for 19 out of the 27 deaths that occurred to respiratory causes (i.e., suggesting that the majority of deaths in this patient group may be directly attributable to bronchiectasis) [10]. Another study identified 5745 NCFBr-related deaths reported in England and Wales between 2001 and 2007, with an estimated 3% annual increase in mortality and approximately 820 deaths per year [13].

#### Prevalence

Data on the prevalence of NCFBr is scant. A recent analysis of the US Medicare database for citizens aged over 65 estimated an 8-year

prevalence of 1106 cases of bronchiectasis per 100,000 [14]. In the UK, a survey of nine specialist centers noted more than 5000 patients with known NCFBr [BILTON D, ROYAL BROMPTON HOSPITAL, PERS. COMM.] as compared with over 8500 patients with CF noted in the UK CF registry (Annual Data Report 2008) [102]. Whereas CF patients are routinely referred to specialist centers in the UK, patients with NCFBr are most likely flagged up to tertiary centers only if their primary physicians find their symptoms difficult to manage in the community. Thus, this figure probably reflects only the proportion of the patient group with the most severe disease and underestimates the true prevalence of the disease; hence, it may be that the prevalence of NCFBr is greater than even that of CF. In the North East of England, the Bronchiectasis Research Interest Network Group (BRING) has a NCFBr patient population of approximately 1100 patients in an area with an overall population of 2.5 million (0.05%) [DE SOYZA A, UNPUBLISHED DATA].

As many more NCFBr patients will be cared for in general respiratory clinics and many cases remain undiagnosed, current prevalence estimates are likely to remain inaccurate. It is likely that NCFBr is as at least as common as CF. Despite this, NCFBr has attracted little in the way of specific clinical commissioning and almost no significant research funding when compared with CF. Collectively, this has led to both patchy service provision and very few evidence-based therapies.

### Natural history

The natural history of bronchiectasis is characterized by clinically 'stable' phases interspersed by exacerbations with a general trend towards a decline in lung function over time; data from a 2-year follow-up study of 76 patients suggests an average of 52.7 ml/year decline in forced expiratory volume in 1 s (FEV<sub>1</sub>) [15]. This is comparable with or worse than rates in COPD [16]. The frequency of exacerbations varies between studies of NCFBr patients; in a number case series, the average number of exacerbations per year varies from 1.5 to 7.4 [17,18]. More frequent exacerbations in NCFBr have the potential to cause a more rapid decline in lung function;  $\geq 1.5$  exacerbations per year was found to be significantly associated with a more rapid decline in FEV<sub>1</sub> [15]. Exacerbations therefore constitute

a significant target in the treatment of bronchiectasis. Thus, the medical management of NCFBr can be divided into two arms: treatment of exacerbations and maintenance therapy (to both improve symptoms and prevent future exacerbations).

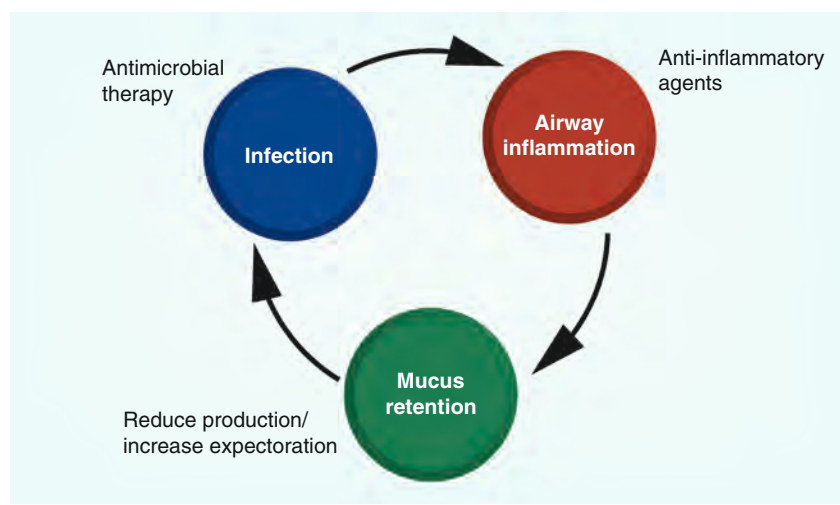
### Principles of therapy

In 1986, Cole introduced the concept of a continuous and self-perpetuating 'vicious cycle' of pathological events responsible for disease progression in bronchiectasis [19]. This cycle of events includes (bacterial) respiratory tract infection with corresponding airway dysfunction and inflammation, the level of which is excessive. Tissue damage follows and leads to impaired mucociliary function. The resulting mucus retention and state of lung injury leaves the host susceptible to further infection and, thus, the cycle repeats. The principles of NCFBr treatment, in order to disrupt this 'vicious cycle', translate to tackling these processes through antimicrobial therapy, anti-inflammatory therapy and attempts to improve bronchial hygiene through reduction of mucus production and/or increasing mucus expectoration (Figure 1). Recent evidence demonstrating that the suppression of bronchial bacterial loads impacts on systemic inflammation supports this 'vicious cycle' hypothesis [20,21].

For those patients with NCFBr who have an identified underlying etiological process with specific targeted treatment potential, such as immunodeficiency and allergic bronchopulmonary aspergillosis, it is clearly also essential to incorporate targeted treatment of this into long-term management plans [7].

### Current practice

The UK national guidelines for the management of NCFBr published by the BTS in 2010 noted significant evidence gaps with many recommendations graded as 'expert consensus' only [7]. The guidelines focused on the use of antibiotics for exacerbations and tackling mucus retention in the stable state. However, the UK guidelines do not always correlate with current clinical practice. This, in part, reflects the inadequate evidence base but also likely illustrates the necessity to individualize treatment to patient needs, such as for those patients who experience overlap syndromes with asthma and COPD.



**Figure 1. The 'vicious cycle' hypothesis of disease progression and corresponding therapeutic targets.**

Adapted from [19].

#### ■ Maintenance therapy

##### Anti-inflammatory & inhaled therapies

The BTS national NCFBr audit in 2011 recently reported findings from 2404 patients collected over a 2-month period in 2011 [103]. Inhaled corticosteroids (ICS) represented the most common prescription for patients (78%). Interestingly, while ICS, particularly combinations of ICS and long-acting  $\beta_2$  agonists (LABAs), are widely used in COPD [22], there are, to date, no compelling data to support their long-term use in bronchiectasis [23]. One recent single-center, randomized controlled trial (RCT) of 40 NCFBr patients treated with combined budesonide–formoterol therapy over 12 months demonstrated some benefit compared with ICS treatment alone [24]. However, recent concerns over the rate of pneumonia in large studies of ICS–LABA in COPD provides a cautionary note for indiscriminate use of ICS–LABA preparations in bronchiectasis [22].

While the role of  $\beta_2$  adrenoceptor agonists is well established in other respiratory diseases, little robust evidence exists in bronchiectasis. Systematic reviews conducted by the Cochrane Collaboration failed to identify any RCTs in bronchiectasis patients that demonstrated the usefulness of inhaled short-acting  $\beta_2$  agonists (SABAs) or LABAs [25,26]. In current UK practice, however, SABAs and LABAs were commonly prescribed (67 and 62%, respectively). Similarly, further Cochrane reviews found no suitable RCTs investigating the role of inhaled

leukotriene receptor antagonists [27], inhaled anticholinergic therapy [28] and oral steroids [29] to inform current practice in the management of bronchiectasis.

##### Mucolytic therapy

Oral mucolytic agents (e.g., carbocisteine) were also noted to be a common pharmacotherapy (30%) in the UK national audit. Although we have experiential evidence that this therapy is effective in our clinic, no convincing RCTs in NCFBr are available. Reflecting this, further studies of mucolytics were recommended in the BTS guidelines for NCFBr. The use of nebulized hypertonic saline (HS) has been advocated in the recent BTS guidelines based on data suggesting that HS use improves sputum viscosity and volume expectorated [30]. No convincing data on the effects of HS on exacerbation frequency are available. As a result, HS does not constitute a common treatment as yet; only 8% of patients were noted to be on this therapy in the UK national audit.

##### Antibiotic strategies

##### Enteral antibiotics

The BTS guidelines suggest that long-term antibiotic use may be appropriate for patients suffering  $\geq 3$  exacerbations a year. This threshold correlates well with the observations of Martínez-García *et al.* in 2007 where  $\geq 1.5$  exacerbations was associated with accelerated lung function decline [15], although there is little evidence to directly attribute an improvement in lung function to long-term antimicrobial therapy as yet. Long-term antibiotic therapy was prescribed to patients in 33% of the recorded observations in the national audit.

The most common choice of antimicrobial agent for long-term therapy was noted to be three-times weekly azithromycin in the 2010 national audit breakdown [31]. Notably, however, it may be prescribed for the anti-inflammatory effects of macrolides, rather than its antimicrobial properties, as might be expected. Two recent RCTs investigating the effects of macrolides, as twice-daily erythromycin and once-daily azithromycin, support the role of long-term, low-dose macrolide therapy in improving the annual rate of infective exacerbations, and possibly FEV<sub>1</sub> values and daily sputum production, although both quote a significantly increased rate of macrolide resistance in treatment groups,

which would hamper its future use in patients [32,33]. Another double-blinded RCT examining the effects of three-times weekly azithromycin also found a significant reduction in exacerbation rate but without an associated improvement in FEV<sub>1</sub> values [34]. Nonetheless, the impact of macrolide therapy (and the preference for their use) may be more a reflection of their ability to act as immunomodulators, predominantly by counteracting neutrophil activity [35], rather than because of their antimicrobial properties. Currently, more specific anti-inflammatory agents are being developed or investigated, including neutrophil elastase inhibitors and non-antibiotic macrolides. Recent concerns over the safety of azithromycin have been raised in the setting of (high-dose) acute therapy for lower respiratory tract infections where a study showed an excess of deaths compared with other (non-macrolide) antibiotics [36]. This finding is, however, of unknown significance to the safety profile of long-term, low-dose therapy.

Cyclical antibiotics given orally on a monthly or 3-monthly basis have not remained a favored maintenance therapy despite early studies supporting their use. Recent data suggests that this approach still holds merit in severe bronchiectasis [7].

#### Parenteral antibiotics

As yet, no inhaled or nebulized antibiotics are licensed for use in bronchiectasis, although 10% of patients reported in the UK national audit received this therapy. The nebulized antibiotics prescribed were colistin (67%), gentamicin (12%) and tobramycin (6%). A RCT investigating inhaled colistin delivered through an 'intelligent nebulizer' has been completed, but is yet to be reported. A recent single-blinded RCT investigating the use of nebulized gentamicin revealed reduced bacterial density in sputum, improved exercise capacity and an improved exacerbation rate with 12 months' therapy, but noted that the effect was lost at 3 months after therapy cessation [37]. A placebo-controlled trial has been conducted in NCFBr patients that showed improvement in sputum bacterial density with nebulized tobramycin [38] but further Phase III trials are required to establish benefits in the clinical setting. Current and emerging trials activity in this area means that new treatments may soon appear but the optimal timing, patient subgroup and duration of therapy remain unclear.

#### Other therapies

The management of NCFBr patients by clinicians may encompass other strategies, including physical training and, for more advanced disease, non-invasive ventilation and surgical resection [7]. While the latter two interventions apply to a select minority, physical training therapies, such as inspiratory muscle training (IMT) and pulmonary rehabilitation (PR; i.e., high-intensity exercise), are suitable for a large proportion of NCFBr patients [103]. Physical training is recommended by the national guidelines for those whose breathlessness impacts on daily activities in order to improve exercise capacity and quality-of-life [7]. However, the evidence is still somewhat limited for either type of physical training. A Cochrane systematic review found only two studies suggesting that IMT may increase exercise tolerance and lung function in NCFBr patients [39] and few other relevant studies have been conducted since. Newall *et al.* found significant improvements in endurance exercise capacity with an 8-week course of PR, but this effect was lost at follow-up unless patients had had concurrent IMT [40].

#### Management of exacerbations

The treatment of exacerbations is usually informed by sputum culture data and initial therapy based on previous specimens. A 5-year follow-up study conducted by King *et al.* found that the most common pathogens isolated from bronchiectasis patients are *Haemophilus influenzae* (47%) and *Pseudomonas aeruginosa* (12%) and noted that these percentages were similar even at follow-up (36 and 16%, respectively) [41]. These results correlate well with other studies (Table 1), including the work of Nicotra *et al.*, who conducted a retrospective analysis of 123 NCFBr patients known to a large University health center in the USA [42], that of Ho *et al.* who performed a prospective cross-sectional study of 100 NCFBr patients recruited from a specialist outpatient clinic in Hong Kong [43] and, finally, that of Pasteur *et al.* who analyzed data from 150 patients presenting to a specialist UK outpatient clinic over a 3-year period [44]. In our local data, using a longitudinal analysis recording any pathogen isolated over an average of 4 years in 167 patients, we found much higher rates of *P. aeruginosa* and *Streptococcus pneumoniae* than the prior cross-sectional studies.



Table 1. Percentage of patients with bacteria cultured from sputum samples.							
Study (year), n	<i>Haemophilus influenzae</i>	<i>Pseudomonas aeruginosa</i>	<i>Streptococcus pneumoniae</i>	<i>Staphylococcus aureus</i>	<i>Moraxella catarrhalis</i>	Other Gram-negative bacilli	Ref.
Nicotra <i>et al.</i> (1995), n = 123	24	45	9	6	2	13	[42]
Ho <i>et al.</i> (1998), n = 100	10	33	6	5	2	5	[43]
Pasteur <i>et al.</i> (2000), n = 150	23	21	9	10	13	11	[44]
King <i>et al.</i> (2007), n = 89 <sup>†</sup>	47	12	7	3	8	2	[41]
De Soyza <i>et al.</i> (2013), n = 167	55	49	36	23	31	51	[UNPUBLISHED DATA]

<sup>†</sup>Results at initial sputum collection.

Other pathogens include *Staphylococcus aureus* and *Moraxella catarrhalis*. Importantly, most studies have been point prevalence and recent data from our center has shown that the period prevalence of culturing *P. aeruginosa* is higher than might be appreciated (Table 1).

Doxycycline or amoxicillin are often the antibiotics of choice in those free from *P. aeruginosa* infection, reflecting the sensitivities of the above prevalent pathogens. Currently, there is a preference for a longer duration of antibiotic therapy and often a higher dose than that for other respiratory conditions (D grade evidence, expert opinion in the BTS guidelines [7]), with 14 days the preferred course length.

Dual-agent antibiotic therapy appears to be less favored for management in NCFBr than for CF patients, in part due to the perception of higher risk of aminoglycoside side effects in the older bronchiectasis population. It is the authors' experience that renal- and oto-toxicity are real and valid concerns in this patient population; this has led us to abandon the routine use of intravenous aminoglycosides.

In current practice, intravenous therapy is often reserved for those refractory to oral antibiotics, particularly those with quinolone-resistant *P. aeruginosa* or for patients with signs of clinical deterioration despite oral antibiotics appropriate to the known sensitivity patterns [7].

Novel therapy  
■ Maintenance therapy

Maintenance therapy in NCFBr, until recently, has been a neglected area for commercially sponsored research. Patients have generally been treated with therapies developed and proven in COPD, asthma and CF, in the hope that these will demonstrate some benefit in NCFBr.

However, within the last few years, there has been a profusion of clinical trials (mostly Phase II) within this area, driven by commercial interests, in part noting the similarities between COPD and NCFBr [2,45]. Mucus hypersecretion, recurrent exacerbations and neutrophilic inflammation are shared pathophysiological processes; the relatively higher exacerbation frequency and neutrophilia seen in NCFBr make it an attractive testbed for proof-of-concept studies of emerging COPD therapies.

Anti-inflammatory therapies

Neutrophil elastase is a protease capable of degrading structural proteins, and is involved in inflammatory processes that can ultimately contribute to lung injury in both acute and chronic respiratory diseases [46]. In bronchiectasis, neutrophil elastase is thought to contribute to the 'vicious cycle' by disrupting neutrophil responses to bacterial organisms and preventing adequate complement activation, thus promoting bacterial growth [47]. Indeed, there are clear data demonstrating the role of injurious levels of neutrophil elastase in the pathophysiology of NCFBr; a recent 1-month placebo-controlled trial (reported in abstract form) of a neutrophil elastase inhibitor in bronchiectasis revealed positive effects both on lung function and quality-of-life [48].

Phosphodiesterase (PDE4) inhibition has shown promise in reducing exacerbation frequency in COPD patients, with some evidence that the effect is best seen in the mucus hyper-secretor/chronic bronchitic phenotype in COPD [49]. While earlier trials with the PDE4 inhibitor, cilomilast, revealed an association with intolerable levels of nausea and vomiting, recent placebo-controlled RCTs investigating

roflumilast, a more selective inhibitor, has shown much improved tolerability among patients (although gastrointestinal symptoms are still common side effects), and further trials in COPD are ongoing. Notably, many moderate-to-severe COPD patients have coexistent bronchiectasis [2,50]. It is unclear if there are plans to study PDE4 inhibition in NCFBr although its benefits in relevant mucus hypersecretor COPD subgroups suggest this approach is certainly worth investigation.

### Mucus clearance

Mucus clearance strategies in the NCFBr population encompass both physiotherapy techniques to physically mobilize mucus, as well as the administration of oral mucolytic agents and inhaled/nebulized hydrating agents; both approaches will be discussed here in more detail.

### Physiotherapy

A small but rigorous crossover RCT conducted by Murray *et al.* in 2009 demonstrated that regular chest physiotherapy, with the Acapella® Choice (Smiths Medical, London, UK) as a mucus mobilization assist device, improved daily expectorated sputum volume, exercise capacity and quality-of-life in NCFBr patients [17]. Prior studies of physiotherapy and physio-assist devices have also been extensively reviewed in recent BTS guidelines. Pragmatically, it appears that although physiotherapy appears beneficial, there is no clear individual technique or device that is suitable for all patients. Consequently, determining the opportunities, physical barriers, comorbidities and lifestyle demands of each patient is essential to enable a satisfactory regimen of daily mucus mobilization exercises and needs to form part of the tailored package of care for each patient. Expert physiotherapists are a key resource to fulfill this treatment requirement.

### Oral mucolytic therapies & inhaled osmotic stimuli

Globally, oral mucolytic agents, such as *N*-acetylcysteine and carbocysteine, have long been used to varying degrees in COPD patients to reduce sputum viscosity (thought, at least in part, due to their ability to disrupt chemical bonds in mucus glycoproteins) [51,52]. As yet, there have been little, if any, significant data on the use of oral mucolytics specific to

bronchiectasis. However, it is noteworthy that mucolytics, in particular carbocysteine, has been shown in large RCTs to reduce exacerbations in COPD [53], although a recent Cochrane review noted large variability in results across trials [51]. Further studies are required to investigate these agents as adjuncts to physiotherapy in NCFBr.

An alternative approach to mucus clearance is to improve the abnormally high mucin-to-airway surface liquid volume ratio such that abnormally thick and adherent mucus is better hydrated and easier to clear from the airway via coughing [54]. Recent research activity has shown some benefit in using inhaled hypertonic saline therapy in NCFBr patients. This includes a single-center, 3-month study that demonstrated that 7% hypertonic saline therapy led to a significant improvement in FEV<sub>1</sub>, number of antibiotics courses used on a yearly basis and quality-of-life scores when compared with 0.9% isotonic saline [55]. However, a 12-month RCT comparing isotonic saline with 6% hypertonic saline found no significant difference between groups, although both were associated with improvements in lung function and quality-of-life in NCFBr patients [56].

Inhaled mannitol, which also acts as an osmotic agent in the airway lumen, hydrating mucus and aiding its expectoration, has been shown to be an effective agent in CF [57]. Early data in NCFBr also shows promise, including that of a large 12-week placebo-controlled trial that showed some non-significant reduction in antibiotic use in the treatment group [58,59]; larger, more robust trials are ongoing, including an investigation of the effect of mannitol on exacerbation rate, and have yet to report outcomes.

### Antimicrobial therapy

Targeting chronic low-grade infection is an attractive option and a number of inhaled or nebulized therapies have shown early promise in NCFBr. Nebulized agents in development include liposomal ciprofloxacin [60], nebulized aztreonam [104] and liposomal amikacin [105]. Furthermore, ongoing developments in dry powder ciprofloxacin, inhaled colomycin, aztreonam–fosfomycin and tobramycin suggest that, in the future, topical antimicrobials will expand the therapeutic options available for NCFBr. Key challenges for inhaled or

nebulized antibiotics in trials will be demonstrating whether reduction in pathogen counts (e.g., reducing colony-forming units) converts into clinically important end points, such as exacerbation frequency reduction, and the optimum duration and timing of therapy. It is possible that only modest or no clinically significant change in FEV<sub>1</sub> should be expected with these antimicrobial therapies [36]. Following experience with nebulized tobramycin use in CF [61], alternating month-on month-off therapy may combine an acceptable adherence/compliance profile in NCFBr with a minimized resistance profile. This, however, has yet to be proven and more robust trials will be needed to define the optimum treatment duration.

In contrast to CF, the microbiology in NCFBr is different with a significantly lower incidence of *P. aeruginosa* infection. Stratifying for *P. aeruginosa* has yet to be widely used in NCFBr studies, yet is clearly a highly relevant consideration given the poorer outcomes and need for hospitalization in those with persistent *P. aeruginosa* infection. It is also unclear if patients chronically infected with mucoid *P. aeruginosa* will respond differently to those infected with non-mucoid *P. aeruginosa* when these emerging therapies are applied. One recent Phase II study investigating inhaled dry powder ciprofloxacin included patients with any of ten predefined pathogens and its full results are eagerly awaited to assess whether responses were markedly different between *P. aeruginosa* and other pathogens [62].

Vaccination against *Pneumococcus* infection and influenza is recommended in the current NCFBr guidelines [7], although to date, there are scant efficacy data in this patient population.

#### ■ Management of exacerbations

Treatment of NCFBr patients during the exacerbation state has rarely been studied in large multicenter trials, with most data limited to investigator-led research [63]. Experiential evidence so far suggests that longer courses of antibiotics of up to 14–21 days may be beneficial but the optimum duration of antibiotic treatment needs to be better defined by robust investigation. Ultimately, there are still several studies that could be performed in the future that would contribute to the optimal management of

NCFBr patients, both during exacerbations and the 'stable' phase (Box 1).

#### Challenges for emerging therapies

There has previously been some nihilism for trials in NCFBr, which arose from the perceived heterogeneity of disease. This is in stark contrast to the enthusiasm for clinical trials in asthma where similar diversity in phenotypes is noted, (e.g., eosinophilic predominant and neutrophilic predominant asthma [64,65]) and for COPD (i.e., bronchitic as compared with emphysema phenotypes [66]).

There is still ongoing debate with regulatory authorities on acceptable outcome measures, and validated bronchiectasis-specific end points are, to date, exceptionally lacking [67]. For example, we have, as yet, not achieved consensus on whether time to next exacerbation or reduction in exacerbations over a time period is the most suitable outcome for NCFBr. In addition, although several objective measures that are currently in use in NCFBr clinical trials appear reasonable, such as improvement in lung function (e.g., FEV<sub>1</sub>) and reduced expectorated sputum volume, there is national acknowledgment that correlations between different end points appear somewhat inconsistent [7]. Patient-related outcome measures or markers of exercise capacity in NCFBr are also still not universally accepted by regulatory authorities. As yet, only two validated patient-related outcome measures exist: the St Georges Respiratory Questionnaire, designed originally for patients with asthma and COPD [68], and the Leicester Cough Questionnaire, which focuses solely on the impact of a chronic cough [69]. A new specifically developed bronchiectasis quality-of-life questionnaire will be most welcome for the clinical community.

Other barriers contributing to the paucity of trials in NCFBr include the incorrect assumption of a declining incidence of NCFBr or lack of a coordinated network of bronchiectasis researchers. Networks of researchers are developing in the UK, the USA, Spain and many other countries. Recently, the US Bronchiectasis Research Registry, supported by the US COPD foundation, recruited its' 1000th patient [106] and similar registries are desperately needed elsewhere. These will not only accelerate patient recruitment into desperately needed trials but also allow mechanistic and genetic association studies to be adequately powered.



**Box 1. Further studies that would be beneficial in non-cystic fibrosis bronchiectasis.****Therapeutic interventional studies that are still required in non-cystic fibrosis bronchiectasis**

- Optimal eradication regimen for *Pseudomonas aeruginosa*
- Large-scale trial of oral mucolytics
- Optimal duration of antibiotics for exacerbations
- Large-scale trials of each of:
  - Inhaled steroids
  - Long-acting antimuscarinics
  - Inhaled long-acting  $\beta$ -agonists
- Large-scale trials of nebulized hypertonic saline therapy
- Optimal dose and duration of oral macrolide therapy

**Conclusion**

The routine management of NCFBr reflects an attempt to disrupt the disease's underlying pathology of a self-perpetuating 'cycle' of infection, airway inflammation and mucus retention. It can be divided into the treatment of infective exacerbations and maintenance therapy (i.e., strategies to improve bronchial hygiene and airway inflammation). Recent national guidelines unfortunately still remain weakly evidence-based and rely heavily on expert consensus opinion due to the lack of research data available in the NCFBr patient population [7]. Current practice, hence, varies among clinicians and often acknowledges therapies used in other chronic respiratory diseases, such as COPD. Some novel therapies are presently under investigation and trial results are eagerly anticipated. However, disease-specific end points and outcomes may still need to be optimized for trial results to be truly applicable to our patient group. Ultimately, this patient group would benefit from increased commercial interest and greater research activity in order to optimize the management of their disease.

**Future perspective**

While the research investment into the management of NCFBr has previously been poor, we are currently in an exciting time of focus, particularly as synergies between aspects of COPD and CF have resulted in a pipeline of drugs that offer promise in NCFBr. We look forward to emerging data from the many agents already under study, including nebulized antibiotics and inhaled mucoactive drugs. This is likely to result in improvement of the number of treatment options available to patients in the near future, such that an overall reduction in

symptom levels is likely to be seen, at least in patients regularly attending specialist clinics to whom novel therapies will be more readily available. There is, however, still a need for more basic science research in NCFBr as underlying pathological processes are still poorly understood and targets for therapy are likely to have been missed. Thus, ultimately, it is likely that many patients may still find their disease suboptimally managed for several years to come.

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