



REVIEW

# What’s new in the management of adult bronchiectasis? [version 1; referees: 2 approved]

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**Abstract**

Bronchiectasis is a heterogeneous, chronic condition with many aetiologies. It poses a significant burden on patients and healthcare practitioners and services. Clinical exacerbations often result in reduced quality of life, increased rate of lung function decline, increased hospitalisation, and mortality. Recent focus in respiratory research, guidelines, and future management options has improved this clinical field in evidence-based practice, but further work and phase III clinical trials are required. This article aims to summarise and explore advances in management strategies in recent years and highlight areas of research and future focus.

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## Introduction

Non-cystic fibrosis bronchiectasis (NCFB) is a chronic inflammatory condition resulting from repeated insult and/or obstruction to small and medium-sized bronchi, leading to fixed dilation and architectural distortion<sup>1,2</sup>. The clinical presentation varies from a chronic, productive, daily cough and recurrent infections to haemoptysis, dyspnoea, and respiratory failure<sup>2,3</sup>.

Bronchiectasis has diverse aetiologies, including idiopathic (up to 50% of cases), post-respiratory tract infection, rare immunodeficiency disorders, genetic abnormalities, autoimmune conditions, chronic inflammation, and mechanical obstruction<sup>2,3</sup>. It is also increasingly being recognised as part of a disease entity coinciding with and complicating other pulmonary conditions such as chronic obstructive pulmonary disease (COPD).

Prevalence rates fluctuate globally, between age groups, and between the sexes and are still largely unknown. However, a recent publication suggests that there is increasing overall incidence and prevalence<sup>4</sup>. In the UK, overall incidence increased from 21 to 35 in women and 18 to 26 in men per 100,000 patient years between 2004 and 2013. The prevalence rates in women increased from 350 to 566 per 100,000 patient years and in men increased from 301 to 485 per 100,000 patient years in the same time<sup>4</sup>. This may be, in part, due to increased diagnosis of the condition and improved computed tomography techniques. The study also illustrated the increased mortality rates in this population group and the need for hospitalisation, further strengthening the case for the increasing impact it has on our healthcare systems<sup>4</sup>.

The mainstay of management is improving symptoms and reducing exacerbations. This article will cover idiopathic and post-infective bronchiectasis in adults and will not include allergic bronchopulmonary aspergillosis (ABPA), cystic fibrosis (CF), immunodeficiency, and non-tuberculous mycobacterium (NTM) disease. It will focus on the therapeutic strategies in bronchiectasis management, particularly highlighting new evidence from between 2013 and 2016.

## The patient-led approach

The first approach to management is to treat the underlying cause if one is identifiable<sup>3,5,6</sup>. British Thoracic Society (BTS) guidelines have a systematic method for screening patients for ABPA, immunodeficiency, CF, and environmental tuberculosis (TB) infection<sup>6</sup>.

The importance of risk stratification has been highlighted in recent years<sup>7,8</sup>. Two main scoring systems have been developed to illustrate severity and mortality – the bronchiectasis severity index (BSI) and FACED<sup>9,10</sup>. Both include FEV<sub>1</sub> (forced expiratory volume in 1 second), dyspnoea, *Pseudomonas* colonisation, and radiological features. They have their limitations, mainly sample size and disparity between mild and moderate phenotypes, but are deemed suitable to predict mortality<sup>9,10</sup>. Additionally, the BSI also includes predictors for hospitalisation and annual mortality risk<sup>9</sup>. These may be useful as adjuncts to decide on clinical management, but further studies are needed to see if such screening systems can be utilised in this way.

The vicious cycle hypothesis was first introduced by Cole and moulds our management interjections<sup>11</sup>. Failure of mucus clearance, persistent infection, and inflammation leading to structural damage are all key aspects. Breaking this cycle by optimising interventions via airway clearance and antibiotic therapy for acute infections has been a backbone of treatment<sup>11</sup>. Broadly categorising therapies into non-pharmacological, pharmacological, and standard and long-term agents, we will explore these aspects and highlight new evidence from the last 3 years.

## Standard therapeutic strategies

### Vaccination

There is an established role for the influenza and pneumococcal vaccinations in the management of chronic respiratory and medical conditions. This is based on limited and low-quality evidence<sup>12</sup>. There have been no recent studies specific to bronchiectasis.

### Airway clearance techniques and pulmonary rehabilitation

Chest physiotherapy forms a core of patient-led management in bronchiectasis irrespective of severity and symptoms. These techniques are patient-centred and variable and aim to aid the removal of secretions from the lung through non-pharmacological methods<sup>13</sup>. Whether these techniques have a clear impact on quality of life or reducing exacerbations has not been adequately proven, and most studies are limited to the CF patient population<sup>13</sup>. Additionally, the use of multidisciplinary exercise interventions (pulmonary rehabilitation [PR]) is seen as an integral part of multimodal management for several chronic diseases<sup>14</sup>. However, much of the data are based on CF or other chronic respiratory conditions. Further randomised controlled trials (RCTs) are required for PR specific to NCFB. **Table 1** summarises the most recent studies and their outcomes for both RCTs.

The recent Cochrane review in 2015 included a total of seven studies in children and adults and a total of 105 patients. Overall, they showed within this limited field that airway clearance techniques (ACTs) are safe in adults and improve certain quality of life measures, lung function, and symptoms<sup>15</sup>. Further studies are required to assess the short- and long-term impact on exacerbations and disease progression.

## Short-term therapy

### Antimicrobial therapy

Fourteen days of antibiotic therapy is recommended for an acute exacerbation of bronchiectasis. The BTS guidelines identify an exacerbation as deterioration in local symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, dyspnoea, and haemoptysis) and or systemic upset<sup>3</sup>.

Intravenous (IV) antibiotics are required when there has been a failure of oral therapy or there is need for hospital admission or *in vitro* resistant pathogens that necessitate IV treatment. There were no studies addressing this. More evidence-based practice for choice and duration of antimicrobial therapy is required. The optimal management of exacerbations remains a vast area of untapped research for robust RCTs and future focus.

**Table 1. Summary of randomised controlled trials (RCTs) for airway clearance techniques (ACTs).**

Non-pharmacological therapy	Study	Study design	Results/outcome	Comments/ adverse events (AEs)	
			Lung function		
			Quality of life		
			Exercise capacity		
			Other		
<b>ACTs and PR</b>	Lee <i>et al.</i> <sup>38</sup>	RCT PR and ACT versus control  43 PR and ACT monitoring 42 unsupervised exercise training but no ACT monitoring  8 weeks	No change in FEV1/FVC at study end	No data	
			Secondary outcome: improved scores – LCQ		
			Primary endpoint: Short-term improvement in exercise capacity (shuttle walk – mean difference to control 62 m, 95% CI 24 to 101 m)		
			No significant difference between exacerbation rates/duration		
<b>ACTs</b>	Nicolini <i>et al.</i> <sup>39</sup>  HFCWO versus chest physiotherapy (CPT) versus medical therapy only	RCT  10 subjects in each group (treatments up to 45 minutes for 5 days per week)  15 days	Secondary outcome: improved lung function ( $p < 0.001$ and $p < 0.006$ )	No AEs	
			Primary endpoint: symptom questionnaires Improvement of 2.7 in BCSS in HFCWO group ( $p < 0.001$ )		
			Increased sputum volume in the HFCWO and CPT group compared with control		

BCSS, breathlessness cough and sputum scale; CI, confidence interval; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; HFCWO, high-frequency chest wall oscillation; LCQ, Leicester Cough questionnaire; PR, pulmonary rehabilitation.

### Eradication therapy

Patients with known *Pseudomonas aeruginosa* (PA) have a reported severe phenotype with increased rates of exacerbation and an independent 3-fold mortality risk<sup>16</sup>. This may be a result of the pathogenicity of the organism and its ability to form biofilms, rendering standard antimicrobial therapies less effective. Therefore, attempted eradication for first isolation is considered reasonable<sup>3</sup>. Further studies are needed to assess 1) if eradication is needed and 2) the optimal management regime.

### Long-term therapies

#### Muco-active therapies

Muco-active therapies can be used for both exacerbations and chronic management. Available as oral, inhaled, or nebulised agents, they reduce sputum viscosity and aid expectoration, thereby theoretically shortening exacerbation length or frequency and improving symptoms<sup>17</sup>.

Although CF and previous studies have shown the potential benefit of hypertonic over 0.9% saline, more recently the evidence

indicates equal efficacy in NCFB<sup>18</sup>. Further studies are required to show whether saline (0.9% or hypertonic) is recommended in practice. Bilton *et al.* studied the effects of inhaled mannitol in a 12-month double-blinded RCT<sup>19</sup>. There was no statistically significant reduction in exacerbation rates; however, there was an improvement in time to first exacerbation and quality of life indicators<sup>19</sup>. The results are summarised in Table 2. Oral agents such as carbocysteine are commonly prescribed in the UK as part of bronchiectasis therapy; however, there are no RCTs to date. Dornase alfa therapy shows an increase in exacerbation rate in NCFB and is not recommended<sup>20</sup>.

#### Anti-inflammatory agents

This broad heading covers many drugs, including corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), leukotriene receptor antagonists, and others. All have different mechanisms of action and vary as either long- or short-term therapy.

**NSAIDs.** There is some evidence to suggest the use of ibuprofen or other NSAIDs in patients with mild CF<sup>21</sup>. There are no studies that support their routine use in non-CF bronchiectasis.

**Table 2. Randomised controlled trial (RCT) on anti-inflammatory and muco-active agents.**

Pharmacological therapy	Study and authors	Study design and intervention	Results Lung function Quality of life Exacerbations Others	Adverse events (AEs) or comments
<b>Anti-inflammatory agents</b>	Mandal <i>et al.</i> <sup>24</sup>  Atorvastatin versus placebo	RCT Placebo-controlled  30 subjects atorvastatin 80 mg OD 30 subjects placebo OD  6 months	Spirometry: no change	Treatment group reported more headaches and gastrointestinal AEs
			Primary endpoint: improvement in cough – LCQ (mean difference 2.2, 95% CI 0.5–3.9; $p=0.01$ )	
			Trend to reduced number of exacerbations	
			Reduced CRP Trend to improved incremental walk test	
<b>Muco-active agents</b>	Bilton <i>et al.</i> <sup>19</sup>  Inhaled mannitol	RCT Placebo-controlled  233 subjects mannitol 400 mg BD 228 control low-dose mannitol  12 months	No endpoint data on lung function	AEs similar between groups
			Secondary endpoint: quality of life SGRQ improved in treatment arm	
			Primary endpoint: annual exacerbation rates No significant reduction 1.69 (95% CI 1.48–1.94) and 1.84 (95% CI 1.61–2.10), $p=0.32$ .	
			Secondary endpoint: time to first exacerbation – improved in mannitol group (165 days versus 124 days [ $p=0.022$ ]) Duration of exacerbations: no change	

6MWT, 6-minute walk test; BD, *bis in die* (twice daily); CI, confidence interval; CRP, C-reactive protein; LCQ, Leicester Cough questionnaire; OD, *omni die* (every day); SGRQ, St George's respiratory questionnaire.

**Leukotriene receptor antagonists.** There are no studies to date for this subset of therapy specific to bronchiectasis.

**Inhaled corticosteroids +/- long acting beta 2 agonists.** The Cochrane review of the long-acting beta<sub>2</sub> agonists (LABA) and inhaled corticosteroids (ICS) combination demonstrated a lack of quality evidence<sup>22</sup>. Only one RCT (2012) was highlighted in the 2014 review evaluating a bronchiectasis adult population without asthma who received inhaled budesonide and formoterol (640µg and 18µg) or high-dose budesonide (1,600µg). The authors found that there was an improvement in dyspnoea symptoms between the combination group and the ICS group<sup>23</sup>. Study size was small and it lacked statistically significant differences in outcomes<sup>23</sup>.

Predominant complications with long-term inhaled therapy are possible pneumonia risk, adrenal suppression, thin skin, and haemoptysis. This risk-benefit profile needs further investigation before management is accepted as routine in the bronchiectasis patient.

### Bronchodilator therapy

**Beta 2 adrenoceptor agonists (short- and long-acting beta agonists).** These agents have been illustrated in clinical trials for asthma and COPD; however, there have been none to date in bronchiectasis. Furthermore, there are no RCTs evaluating the use of inhaled anticholinergics. The role of bronchodilator therapy in bronchiectasis is unproven but often used in clinical practice with the breathless patient. If there is subjective improvement, it is sensible to continue such treatment.

### Other long-term therapies

Mandal *et al.* reported the use of atorvastatin versus placebo with the primary endpoint of reducing cough<sup>24</sup>. Over a 6-month study period, the use of atorvastatin was shown to improve cough on quality of life questionnaire<sup>24</sup>; the results are discussed in [Table 2](#).

Neutrophil elastase (NE) is a protease involved in inflammatory processes that has the ability to cause lung damage. It shows

an increased activity in bronchiectasis. AZD9668 is an orally available NE inhibitor studied in a randomised, double-blinded, placebo-controlled phase II study by Stockley *et al.*<sup>25</sup>. A total of 16 patients were randomised to placebo and 22 to treatment for 28 days<sup>25</sup>. There was no statistical significance in sputum neutrophil count or weight. Secondary endpoint of quality of life questionnaire showed a clinical difference suggestive of benefit, but the results did not meet significance<sup>25</sup>. Further studies on similar novel agents are encouraged in order to broaden our scope for long-term anti-inflammatory treatments.

### Macrolides

The use of chronic macrolide therapy has been described for many respiratory conditions. The mechanism of action has been the point of research topics and includes anti-inflammatory, immunomodulatory, and antimicrobial actions. Their chronic use has been noted within the diffuse panbronchiolitis and CF populations<sup>26</sup>. This has spurred clinical trials in the bronchiectasis group.

Three major studies in 2012 and 2013 from Australia, New Zealand, and the Netherlands compared azithromycin daily, azithromycin three times weekly, and low-dose erythromycin and have led the way in establishing macrolide use in long-term bronchiectasis therapy<sup>27–29</sup>. Despite the publication date, all three studies (BLESS, BAT, and EMBRACE) have been included in this report because of their significance in current bronchiectasis management. The three trials reported their primary outcome as exacerbation frequency, and they have illustrated significant reduction in exacerbation rates<sup>27–29</sup>. There was some benefit in quality of life measures but a clinically insignificant improvement in lung function; [Table 3](#) summarises the results.

Although long-term antibiotics are still not recommended on a routine basis, in a selected group based on frequent exacerbations (three or more per annum) or fewer exacerbations but increasing morbidity, this intervention should be considered. However, we must balance this with the possible emergence of antibiotic resistance and possible cardiovascular, audiological, and gastrointestinal adverse events (AEs). A practical but prudent issue is the necessity to screen these patients for NTM infection prior to embarking upon long-term macrolide therapy, as this would have potential consequence on NTM management<sup>30</sup>.

The prospect of non-antimicrobial therapies and novel anti-inflammatories exposes an exciting area for future phase II and III clinical trials.

### Inhaled or aerosolised antibiotic or other therapies

With the burden of antimicrobial resistance increasingly real and a global political agenda for stewardship, the need for enhancing techniques and the delivery of antimicrobials responsibly with

reduced adverse effects is paramount. Aerosolised and inhaled delivery within the lung has been of interest, as high concentrations of drug can be administered within the airways with reduced systemic side effects. The basis for inhaled antibiotics in bronchiectasis has not yet been established in clinical trials; however, recent work is exposing an exciting field. Currently, there are no approved inhaled antibiotics licensed for use by UK, European, or USA drug agencies for bronchiectasis.

Barker *et al.* studied the effects of inhaled aztreonam in bronchiectasis patients in two double-blinded, randomised, placebo-controlled trials<sup>31</sup> ([Table 3](#)). Their primary endpoint of quality of life did not reach statistical significance, and they also reported more treatment-related AEs<sup>31</sup>.

[Table 3](#) illustrates several RCTs analysing the safety and effect of inhaled or nebulised agents in long-term therapy. Haworth *et al.* studied the effectiveness of inhaled colistin for up to 6 months within 21 days of an exacerbation<sup>32</sup>. Although they did show a difference in the median time to first exacerbation, it did not reach statistical significance. However, improvements in secondary endpoints of bacterial density and quality of life did. This study also illustrated the importance of adherence, and, when taking more than 80% of therapy, it did improve the time to first exacerbation significantly<sup>32</sup>.

There are two phase III trials of inhaled ciprofloxacin, RESPIRE-1 and -2, that have now been completed with the results awaited. They have two regimens comparing 28 days on and off for 1 year versus 14 days on and off for 1 year. A competitor study has utilised liposomes to allow slow release of ciprofloxacin and molecular stability in nebulisation and to improve delivery to macrophages<sup>33,34</sup>. Successful phase II studies of liposomal ciprofloxacin (pulmaquin) have shown a significant reduction in PA colony-forming units (CFUs) in sputum compared with placebo<sup>35</sup>. Subsequent to this, two identical international studies have completed enrolment to a phase III study (ORBIT-3 and -4)<sup>36,37</sup>. The primary endpoint will be evaluation of time to first exacerbation, and secondary endpoints include quality of life measures<sup>37</sup>. Overall, the initial results are encouraging, prove tolerability, and promise a potential inhaled therapy for bronchiectasis ([Table 3](#)). The full reported results of ongoing phase III studies in inhaled ciprofloxacin and nebulised ciprofloxacin with liposomal technology are eagerly awaited.

### Summary

There has been increased research activity in the field of bronchiectasis owing to its growing burden on healthcare systems secondary to reported increased prevalence. However, the quality of evidence in the field remains limited owing to the lack of RCTs. Long-term RCTs are greatly needed to further this field and improve patient outcome.

**Table 3. Summary of randomised controlled trials (RCTs) for long-term oral, inhaled, and nebulised antimicrobial therapies.**

Pharmacological therapy	Study and authors	Study design and intervention	Results Lung function Quality of life Exacerbations	Adverse events (AEs) or comments
<b>Long-term macrolide therapy</b>	BAT (bronchiectasis and long-term azithromycin treatment) Altenburgh <i>et al.</i> <sup>27</sup>	RCT Double-blinded Placebo-controlled 43 azithromycin 250 mg OD 40 matching placebo 12 months	Secondary endpoint: FEV <sub>1</sub> 3-monthly increased by 1.03% in treatment group and decreased by 0.10% in placebo group ( $p=0.47$ ) Secondary endpoint: SGRQ improved by 6 units per 6 months in treatment group and 2 units in placebo group ( $p=0.046$ ) Primary endpoint: median number of exacerbations in 12 months Azithromycin group 0, placebo group 2 ( $p < 0.001$ )	GI AEs: 40% in treatment group and 5% in placebo group Macrolide resistance to oropharyngeal flora: 88% in treatment group and 26% in placebo group oropharyngeal flora
	Azithromycin versus placebo BLESS (bronchiectasis and low-dose erythromycin study) Serisier <i>et al.</i> <sup>28</sup>	RCT Double-blinded Placebo-controlled 59 subjects 400 mg BD erythromycin 58 subjects matching placebo 12 months	Secondary outcome: reduction in rate of decline of FEV <sub>1</sub> No statistically significant difference Secondary endpoint: SGRQ -1.3 units in placebo group and -3.9 units in treatment group; no statistically significant difference Primary endpoint: annualised mean rate of exacerbations Statistically significant reduction: mean 1.29 [95% CI 0.93-1.65] versus 1.97 [95% CI 1.45-2.48] erythromycin versus placebo	Statistically significant increase in macrolide resistance (oropharyngeal flora) in treatment vs. placebo group (secondary endpoint)
	Erythromycin versus placebo EMBRACE (azithromycin for the prevention of exacerbations) Wong <i>et al.</i> <sup>29</sup>	RCT Double-blinded Placebo-controlled 71 subjects azithromycin 500 mg M/W/F 70 subjects placebo equivalent 6 months	Co-primary endpoint: FEV <sub>1</sub> before bronchodilator There was no statistically significant difference Co-primary endpoint: SGRQ No statistically significant difference between groups at 12-month follow up Primary endpoint: exacerbation rate 42 event-based exacerbations in treatment group versus 102 in placebo group. Rate was 0.59 in treatment group versus 1.57 in placebo group (rate ratio 0.38, 95% CI 0.26-0.54; $p < 0.0001$ ).	More frequent GI side effects in treatment group No routine macrolide resistance testing
	Azithromycin versus placebo ORBIT II (once-daily respiratory bronchiectasis inhalation treatment) Serisier <i>et al.</i> <sup>35</sup>	RCT Double-blinded Placebo-controlled 20 subjects dual release ciprofloxacin for inhalation via nebuliser 3 cycles versus placebo 22 OD 3 cycles 28 days	No difference in FEV <sub>1</sub> No difference in quality of life (SGRQ) Secondary endpoint: increased time to first exacerbation Median 134 versus 58 days, $p=0.057$ (nITT) but 0.046 (per protocol) Primary endpoint: Mean (SD) 4.2 (3.7) log <sub>10</sub> CFU/g reduction in PA bacterial density at day 28 (versus -0.08 [3.8] with placebo) $p=0.002$	No difference in AEs
	Inhaled and nebulised antimicrobial therapy	Inhaled ciprofloxacin versus placebo		

Pharmacological therapy	Study and authors	Study design and intervention	Results Lung function Quality of life Exacerbations	Adverse events (AEs) or comments
	ORBIT III and IV (NCT01515007 and NCT02104245) O'Donnell <i>et al.</i> <sup>37</sup> Dual-release inhaled pulmaquin	RCT Double-blinded Placebo-controlled 584 subjects randomised 6 cycles of 28 days on and off over 48 weeks	Secondary endpoint: quality of life Primary endpoint: time to first exacerbation – results to be published Secondary endpoints: number of exacerbations/severe exacerbations	
	RESPIRE I De Soyza <i>et al.</i> <sup>34</sup> Inhaled ciprofloxacin	RCT Double-blinded Placebo-controlled Ciprofloxacin DPI 32.5 mg versus placebo 416 patients randomised 2 regimens: 14 days on/off or 28 days on/off for 48 weeks	Primary endpoint: time to first exacerbation Significant prolongation in treatment versus placebo group ( $p=0.0005$ ). Reduced frequency of exacerbations ( $p=0.0061$ ).	No significant difference in adverse drug reactions between both groups reported in abstract
	AIR-BX1 AIR-BX2 Barker <i>et al.</i> <sup>31</sup> Inhaled aztreonam versus placebo	RCT x 2 Double-blinded Placebo-controlled 1) 134 AZLI 75 mg TDS for 4 weeks with 4 week off periods, 132 placebo 2) 136 AZLI and 138 placebo 75 mg TDS for 4 weeks with 4 week off periods 2 cycles	Primary endpoint: reduction in bronchiectasis symptoms (QOL-B-RSS) No difference in AIR-BX1. Difference in AIR-BX2: 4.6 (1.1 to 8.2), $p=0.011$ .	More AEs (increased cough, sputum, and dyspnoea) reported in treatment versus placebo
	Wilson <i>et al.</i> <sup>40</sup> Inhaled ciprofloxacin DPI versus placebo	RCT Double-blinded Placebo-controlled 60 subjects ciprofloxacin DPI 32.5 mg BD 64 subjects BD placebo 28 days	Secondary endpoint: Treatment $FEV_1$ improves by $0.06 \pm 8.36\%$ Placebo $FEV_1$ decreased by $-0.40 \pm 10.36\%$ No statistically significant difference Secondary endpoints: improvement in SGRQ Adjusted mean difference between treatment and placebo was $-3.56$ (95% CI $-7.3-0.1$ , $p=0.059$ ) 22 treatment subjects versus 25 placebo reported $\geq 1$ exacerbation Primary endpoint: reducing bacterial load Significant reduction in CFU ( $-3.62 \log_{10}$ CFU/g, range $-9.78-5.02 \log_{10}$ CFU/g) versus placebo ( $-0.27 \log_{10}$ CFU/g, range $-7.96-5.25 \log_{10}$ CFU/g; $p < 0.001$ )	50 versus 54 in placebo of any reported AEs



Pharmacological therapy	Study and authors	Study design and intervention	Results Lung function Quality of life Exacerbations	Adverse events (AEs) or comments
	RESPIRE 1 and 2 (NCT01764841) Inhaled ciprofloxacin versus placebo	RCT Double-blinded Placebo-controlled  Ciprofloxacin inhaler BD 14 days and 28 days versus placebo (on and off period)  12 months	Results to be published  Secondary endpoints: FEV <sub>1</sub> , quality of life (SGRQ), number of exacerbations, eradicated and new pathogens  Primary endpoint: time to first exacerbation	Results to be published
	Haworth <i>et al.</i> <sup>32</sup> Nebulised colistin versus nebulised saline	RCT Double-blinded Placebo-controlled  73 colistin 1 million IU BD 71 placebo (0.45% saline) BD  6 months	FEV <sub>1</sub> , mean differences at 4, 12, and 26 weeks: -0.05, -0.11, and -0.10L Treatment differences: no statistical significance 95% CI -0.17 to 0.07, -0.17 to 0.07, and -0.22 to 0.02 SGRQ at baseline, week 12, and week 26 Mean difference at 12 weeks' colistin: -2.8 Units and placebo -2.2 Units Week 26 colistin: -10.4 and placebo -0.4 Reached statistical significance at week 26 (p=0.006)  Primary endpoint: time to first exacerbation Median time 168 days with colistin versus 103 days with placebo (p=0.038) in adherent patients Importance of adherence emphasised  Secondary endpoints: severity of exacerbations, adherence, sputum weight, and CFUs of PA Significant reduction in PA density in treatment group versus placebo group	Total 143 AEs in treatment versus 108 in placebo. Five colistin patients withdrew because of bronchoconstriction

AZLI, aztreonam for inhalation solution; BD, *bis in die* (twice daily); CFU, colony-forming units; CI, confidence interval; DPI, dry powder for inhalation; FEV<sub>1</sub>, forced expiratory volume in 1 second; GI, gastrointestinal; IU, international unit; OD, *omni die* (every day); PA, *Pseudomonas aeruginosa*; QOL-B-RSS, quality of life-bronchiectasis respiratory symptoms score; SGRQ, St George's respiratory questionnaire; TDS, *ter die sumendum* (three times a day).

## Competing interests

The authors declare that they have no competing interests.


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