

# Advances in bronchiectasis

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## ABSTRACT

**Bronchiectasis is a chronic inflammatory condition with a diverse aetiology including recurrent infections, genetic abnormalities, immunodeficiency and autoimmune disorders. The prevalence has increased over the past few years and this may be due to better imaging and diagnostic techniques. Management remains the emphasis for improving symptoms and reducing exacerbations. This article focuses on highlighting the latest data released since 2014 on new diagnostic techniques as well as potential future pharmacological and non-pharmacological treatment options for patients with bronchiectasis.**

## Background

Bronchiectasis is a heterogeneous condition, which presents a significant burden to the healthcare system not only in terms of its chronicity but also due to its increasing prevalence. It occurs as a result of repeated insults to the lower respiratory tract, altered muco-ciliary clearance that leads to stasis of secretions, infection, inflammation and eventually destruction and dilatation of the peribronchial and bronchial tree.<sup>1</sup> This article discusses recent advancements from 2014 made in the diagnosis and long-term management of bronchiectasis.

## Method

We carried out a PubMed search for studies published from 2014 to the January 2019 for advances in diagnostic and management strategies in bronchiectasis. We also searched the Cochrane Database Systematic Review on pharmaceutical management of bronchiectasis. The main primary outcomes we looked at included time to first exacerbation, frequency of exacerbations and impact on quality of life.

## Diagnostic techniques for assessing the sputum microbiome

Conventional culture techniques are restricted by the quality of sputum provided, lack of sensitivity in detection of pathogens and the duration of time it takes to obtain results which is usually 48 hours or longer.<sup>2</sup> Cox *et al* analysed the longitudinal

variability of the microbiome in the sputum of bronchiectasis patients with respect to clinical variables. 16S rRNA sequencing was carried out on sputum microbiota of 381 sputum samples from 76 patients and demonstrated that microbial communities were unique in their composition, stability and often contained multiple pathogens. Also, microbial culture had limited sensitivity in identifying common pathogens including *Pseudomonas aeruginosa* and *Haemophilus influenzae* compared to deoxyribonucleic acid sequencing. Furthermore, there was a poor correlation between community characteristics with clinical features including underlying disease and even antibiotic use. Therefore, the study concluded that there is an urgent need for revision of principles for antimicrobial therapy in bronchiectasis patients by giving targeted therapy to the individual's microbiome and taking into account important factors such as community stability and pathogen load.<sup>3</sup> Molecular techniques offer higher

## Key points

Sputum for routine microbiology culture is the current recommendation but molecular techniques offer higher sensitivity in detection of bacterial pathogens from sputum samples and may be used in the future if the process time is shortened, interpretation of the complex microbiome is facilitated and cost is reduced.

A trial of long-acting inhaled bronchodilators is warranted in patients with bronchiectasis that complain of breathlessness.

In the UK, we use nebulised colomycin as a first-line and gentamicin as a second-line treatment for patients with chronic infection with *Pseudomonas aeruginosa* with three or more antibiotic-requiring exacerbations per year.

Preliminary studies show beneficial effects of statin therapy, but multi-centred studies are needed before they can be recommended for routine use.

Inhaled corticosteroids are not routinely recommended in patients with bronchiectasis, unless there are other indications, such as co-existing asthma.

**KEYWORDS:** Bronchiectasis, long-term antibiotics, inhaled or oral steroids, airway clearance, bronchodilators ■

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sensitivity in detection of bacterial pathogens but currently the long process time for a result and cost limits its use in routine practice.

### Long-term antibiotics – role of inhaled/nebulised antibiotics

The RESPIRE trials were two major, double-blind, placebo-controlled phase III studies which analysed the efficacy and safety of ciprofloxacin dry powder for inhalation (DPI) in patients with bronchiectasis who had two or more exacerbations in a year and potential pathogenic organisms present in sputum. RESPIRE I showed that ciprofloxacin DPI given for two weeks on and off for a 48-week period resulted in delay in time to first exacerbation which was statistically significant compared to pooled placebo with a median time of more than 336 versus 186 days (hazard ratio (HR) 0.53, 97.5% confidence interval (CI) 0.36–0.8,  $p=0.005$ ). In RESPIRE II, there was a reduction in frequency of exacerbation seen in the arm where patients were given ciprofloxacin DPI on/off for 28 days (incidence ratio 0.55, 99.9% CI 0.3–1.02,  $p=0.0014$ ).<sup>4,5</sup> Although inhaled ciprofloxacin was well tolerated by patients, due to the inconsistencies between these trials, inhaled ciprofloxacin remains unlicensed for use in patients with bronchiectasis.

A phase II trial of liposomal ciprofloxacin (Pulmaquin) called ORBIT 2 demonstrated a significant reduction in bacterial load, with a reduction in *Pseudomonas* colony forming units in sputum compared to placebo.<sup>5</sup> Thereafter, ORBIT 3 and 4 were two parallel multi-national, double-blind, randomised, placebo-controlled phase III trials where patients either received Pulmaquin or placebo over a 48-week period. In ORBIT 4, the median time to first pulmonary exacerbation was 230 days in the Pulmaquin group compared with 158 days in the placebo group. There was a statistically significant difference of 72 days (HR 0.72, 95% CI 0.53–0.97,  $p=0.032$ ). However, in ORBIT 3, the median time to first exacerbation was 214 days in the Pulmaquin group and 136 days in the placebo group but the difference was not significant. In pooled analysis of both trials the median time to first pulmonary exacerbation was not found to be statistically significant (HR 0.82, 95% CI 0.65–1.02,  $p=0.074$ ). Therefore, due to the inconsistency between the trials liposomal ciprofloxacin remains unlicensed treatment for bronchiectasis.<sup>6</sup>

The AIR-BX1 (266 patients) and AIR-BX2 trials (274 patients) studied nebulised aztreonam compared to placebo. Nebulised aztreonam was given at 75 mg three times a day or placebo for 1 month on and 1 month off during a 4-month period. The primary end point was change from baseline in the quality of life bronchiectasis questionnaire respiratory symptom scores at 4 weeks. This was not significant with aztreonam treatment at 4 weeks (HR 0.8, 95% CI -3.1–4.7,  $p=0.68$ ) in AIR-BX1, it was significant (HR 4.6, 95% CI 1.1–8.2,  $p=0.011$ ) in AIR-BX2, but did not meet the minimal important clinical difference. The most common reported treatment-emergent adverse events were dyspnoea, cough and increased sputum. Nebulised aztreonam remains an unlicensed treatment for bronchiectasis.<sup>7</sup>

Both the RESPIRE and ORBIT trials showed inconsistencies in findings between two identical studies and the reason for these could be multi-factorial including differences in geographical location between the first and second trial, the definition of exacerbation used in order to ascertain eligibility for the trials and the variability in severity of disease in recruited patients. The British Thoracic Society (BTS) guidelines recommend considering

long-term antibiotics, in patients needing three or more courses of antibiotics per year. Patients selected for inhaled/nebulised antibiotics should predominantly be those chronically infected with *P aeruginosa*. First line treatment is nebulised colomycin 1 MU twice daily and second line nebulised gentamicin 80 mg twice daily.<sup>8</sup>

### Long-term antibiotics – role of macrolide therapy

A recent systematic review by Kelly *et al* published in 2018 which included 14 parallel group randomised controlled trials (RCTs) and a cross-over RCT found that macrolides reduced frequency of bronchiectasis exacerbations more than placebo (odds ratio (OR) 0.34, 95% CI 0.22–0.54; 341 participants; three studies;  $I^2$  65%; moderate-quality evidence). Patients on macrolides were shown to have a better quality of life compared to placebo according to their St George's Respiratory Questionnaire score (median difference 8.9, 95% CI -13.13–4.67; 68 participants; one study; moderate-quality evidence). There was no difference found in serious adverse events (pneumonia, respiratory and non-respiratory infections, haemoptysis, and gastroenteritis) between macrolides and placebo groups (OR 0.49, 95% CI 0.2–1.23). Limited data is available on possible associated increased antibiotic resistance.<sup>9</sup>

A systematic review published in 2017 by Li W *et al* carried out an adjusted indirect treatment comparison (AITC) between macrolides. The direct comparison meta-analysis found macrolides reduced rate of exacerbation (relative risk (RR) 0.45; 95% CI 0.36–0.55) with heterogeneity ( $I^2$  63.7%,  $p=0.064$ ) and that azithromycin showed lower exacerbations rates than erythromycin (RR 0.35, 95% CI 0.403–0.947). Azithromycin was also associated with an increased risk of diarrhoea and abdominal pain.<sup>10</sup>

BTS guidelines recommend ensuring there is no active non-tuberculous mycobacterium infection on culture. Long-term macrolides should be used with caution in patients with hearing loss or significant balance issues. Doxycycline is considered an acceptable alternative in patients who cannot tolerate macrolides or they have not been effective. For patients with bronchiectasis on long-term antibiotics, it is preferred for them remain on the same antibiotics rather than rotate between different antibiotic classes.<sup>8</sup>

### Role of long-term anti-inflammatory therapies – statin treatment

The latest BTS guidelines acknowledge that recent studies have demonstrated that statins have multiple anti-inflammatory and immunomodulatory effects in addition to lowering cholesterol.<sup>8</sup> A small double-blind cross-over RCT by Bedi *et al* analysed the effects of statin therapy in patients with severe bronchiectasis who are chronically infected with *P aeruginosa*. The atorvastatin arm did not show a significant improvement in the primary end point of cough which was measured by Leicester Cough Questionnaire (LCQ) score (mean difference 1.92, 95% CI for difference -0.57–4.41,  $p=12$ ). However, atorvastatin treatment did show an improvement according to St George's Respiratory Questionnaire (-5.62 points;  $p=0.16$ ). There was some improvement noted in serum C-reactive protein and serum neutrophil counts ( $p=0.07$  and  $p=0.06$ , respectively). Therefore, overall the study demonstrated that atorvastatin decreased systemic inflammation and showed

some improvement in the quality of life of patients infected with *P aeruginosa* which may be related to the ability of atorvastatin to modulate activation of neutrophils.<sup>8,11</sup>

Another RCT by Mandel *et al* allocated 30 patients to high dose atorvastatin at 80 mg once a day and 30 patients to placebo for a period of 6 months. In total, 12 patients (40%) in the atorvastatin group improved by 1–3 units or more on the LCQ in comparison to five patients (12%) in the placebo group (difference 23%, 95% CI 1–45,  $p=0.04$ ). The mean change in LCQ score was of 1.5 units in patients allocated atorvastatin versus -0.7 units in those assigned placebo (mean difference 2.2, 95% CI 0.5–3.9,  $p=0.01$ ). There was a reduction seen in the number of exacerbations, however, no statistically significant impact was made on mean exacerbations. Multicentre studies are required to determine if long-term statins can reduce the exacerbations in patients with bronchiectasis.<sup>12</sup>

### Inhaled bronchodilator therapy

A RCT of 40 patients in 2014 compared budesonide/formoterol versus budesonide in bronchiectasis patients. The study claimed the use of the combination inhaler improved quality of life of patients with bronchiectasis, however, a later Cochrane review found significant problems with the trial model, including incorrect blinding and reporting of data.<sup>12</sup> There have been no further RCTs that evaluate effects of short- or long-acting beta agonists or indeed anticholinergic agents in patients with bronchiectasis.<sup>8</sup>

BTS guidelines recommends following asthma and chronic obstructive pulmonary disease (COPD) guidelines for using long-term bronchodilators for bronchiectasis patients with significant symptoms of breathlessness and co-existing asthma and COPD. In those without comorbid asthma or COPD, to offer a trial of long-acting bronchodilator therapy in patients with symptoms of significant breathlessness. Reversibility testing to beta 2 agonist or anticholinergic bronchodilators may help to identify patients with co-existing asthma but there is no evidence to suggest that a response is required in order to benefit from bronchodilators.<sup>9</sup>

### Long-term inhaled or oral corticosteroids

There have been no recent RCTs looking at the efficacy of inhaled or oral corticosteroids in patients with bronchiectasis since 2014. BTS guidelines do not recommend offering inhaled or oral corticosteroids to patients with bronchiectasis unless there are other indications such as asthma, COPD, allergic bronchopulmonary aspergillosis and inflammatory bowel disease.<sup>8</sup>

### Airway clearance

Airway clearance technique is an important non-pharmacological and patient-centred part of management in patients with bronchiectasis. Lee *et al* published the results of an RCT (85 patients) in 2014 which compared pulmonary rehabilitation and review of airway clearance technique versus placebo over eight weeks.<sup>14</sup> There was a short-term improvement seen in exercise capacity (shuttle walk – mean difference to control 62 m, 95% CI 24–101 m) at 8 weeks not maintained at 6 or 12 months. Exercise training reduced the frequency of acute exacerbations (median 1, interquartile range (IQR) 1–3) compared to the control group (median 2, IQR 1–3) over 12 months follow-up ( $p=0.012$ ), with a longer time to first exacerbation with exercise training of 8 months

(95% CI 7–9 months) compared to the control group (6 months, 95% CI 5–7 months,  $p=0.047$ ).

A systematic review by Hill *et al* in 2018 looked at non-pharmacological methods in treatment of cough in patients with both CF and non-CF bronchiectasis. The review found that no large randomised trials analysed the impact of airway clearance on rate of exacerbation, quality of life, hospitalisation rates or mortality.<sup>15</sup>

The BTS guidelines encourages teaching all individuals with bronchiectasis to perform airway clearance by a respiratory physiotherapist. The commonest technique used is the active cycle of breathing technique and to consider gravity assisted positioning, unless contraindicated, in order to enhance airway clearance technique. Adjuncts are considered (normal or hypertonic saline) or oral agents such as carbocisteine in those with frequent chest infections, despite regular airways clearance. There is a lack of RCTs to support this, however, in bronchiectasis to date. Patients admitted with an exacerbation of bronchiectasis should be seen daily by a respiratory physiotherapist until their airway clearance is optimised.<sup>8</sup>

### Conclusion

There is a lack of licensed therapies in bronchiectasis and multi-centred RCTs are needed to support evidence-based therapies to improve symptoms and reduce exacerbations in patients with bronchiectasis. ■

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