EXPERT OPINION

Developing drug therapies in bronchiectasis

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Introduction: Bronchiectasis is a chronic respiratory condition characterised by cough, sputum production and recurrent chest infections. There are multiple aetiologies; but in up to 50% of patients, the aetiology is unknown. The treatment is largely symptomatic with regular chest physiotherapy and antibiotics for infective exacerbations. Research is being directed towards breaking the 'vicious circle' of bronchiectasis with therapies directed at improving mucociliary clearance, treating chronic infection and reducing inflammation in the airways.

Areas covered: This review highlights the current status of bronchiectasis research, summarising reported and ongoing studies of potential therapeutic agents not yet assessed in large trials or licensed for treatment. A literature review was performed using the PubMed database and upcoming trials were sought on the ClinicalTrials.gov website. The article is limited to studies in preclinical to Phase II clinical trials. The trials highlighted in this article offer insight into potential therapeutic agents for the future and help highlight areas in need of further targeted research.

Expert opinion: There are promising new anti-infective and anti-inflammatory therapies for more advanced bronchiectasis. That being said, Phase III studies are still needed to investigate these agents further, as well as at what stage therapy should be implemented.

Keywords: antibiotics, anti-inflammatory, bronchiectasis, mucoactive, pharmacotherapy

Expert Opin. Investig. Drugs (2015) 24(2):169-181

1. Introduction

Bronchiectasis is a chronic respiratory condition first described over a century ago, characterised by daily cough and chronic sputum production with a predisposition to recurrent chest infections [1]. The prevalence of bronchiectasis is unknown but it is being recognised and diagnosed more commonly, perhaps because high-resolution computer tomography (CT) scanning of the chest, the gold standard for diagnosis, is more frequently used in clinical practice. In the USA, the prevalence ranges from 4/100,000 in young adults to nearly 300/100,000 in those > 75 years [2,3]. Diagnostic CT images show the bronchial diameter to be larger than the adjacent pulmonary artery in affected areas (signet ring sign). The degree of bronchial dilatation increases with severity from cylindrical or tubular bronchiectasis in mild disease to varicose bronchiectasis (focal constrictive areas along the dilated airways) to saccular or cystic bronchiectasis in severe disease [4].

The spectrum of bronchiectasis ranges from mild, moderate to severe. The classification of bronchiectasis is complex and there is a degree of overlap. The severity should be classified based on clinical phenotype and not purely based on CT appearances. In our clinical experience, mild disease is associated with the following clinical features: mucoid sputum production when stable, < 10 ml sputum volume/24 h and limited exacerbations (1 or 2 exacerbations a year), which can usually be treated with oral antibiotics. Moderate disease is usually associated with mucopurulent or purulent sputum when clinically stable but not leading to an

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10.1517/13543784.2015.971153 © 2015 Informa UK, Ltd. ISSN 1354-3784, e-ISSN 1744-7658

Article highlights.

- Bronchiectasis has become more commonly recognised with the advent of computer tomography of the chest.
- The mainstay of treatment for clinically significant bronchiectasis is chest physiotherapy and antibiotics.
- Large randomised controlled trials are lacking in bronchiectasis.
- Encouraging data has been published in mucoactive therapies, long-term antibiotics and anti-inflammatory therapies.
- Larger randomised controlled trials are needed to identify long-term effects of such therapies and target groups for long-term therapy.

This box summarises key points contained in the article.

excess of exacerbations (≤ 2 exacerbations a year). Patients with severe disease have frankly purulent sputum when clinically stable produce more than 10 ml/day and have more frequent exacerbations (≥ 3/year). These patients can be colonised by more difficult pathogens such as *Pseudomonas aeruginosa*, other enteric Gram-negative organisms or MRSA. These patients may require intravenous antibiotics and hospital admission to treat their exacerbations [1,5].

Bronchiectasis has been termed an 'orphan disease' relating to the relative lack of research in this field when compared to asthma, lung cancer and chronic obstructive pulmonary disease (COPD) [6]. Bronchiectasis is often regarded as a heterogeneous disease in view of the multiple aetiologies and associated comorbidities. About 53% of cases are idiopathic and the second most common cause is a past respiratory infection (29 – 42%) [1,7,8].

Cole coined the phrase 'the vicious circle' when describing the pathogenesis of bronchiectasis [9]. The colonisation of lower respiratory tracts with pathogenic bacteria leads to a predominantly neutrophilic inflammatory response in the airways. Despite this host response, there is a failure of bacterial clearance [5,10]. The neutrophil products, in particular neutrophil elastase, can further damage the mucociliary escalator, predisposing to bacterial colonisation which perpetuates the inflammatory response. Thus, the vicious circle is established [9].

Therapies designed to break this circle can be grouped into anti-infective, anti-inflammatory and mucoactive agents. The goals of treatment include reducing cough and sputum volume, reducing sputum purulence, reducing the number of chest infections and improving quality of life (QofL).

This review on developing therapies summarises the trials in preclinical to Phase II stages of new drugs being explored for the treatment of idiopathic and post-infection bronchiectasis. It is beyond the scope of this paper to comment on treatment strategies for bronchiectasis due to active allergic bronchopulmonary aspergillosis, active sarcoid, cystic fibrosis (CF) and immunoglobulin deficiencies, all of which have their own disease-specific treatments.

A literature search was performed on PubMed with the following keyword searches: 'bronchiectasis' or 'non-cystic fibrosis bronchiectasis' and 'Phase I study', 'Phase II study', 'antibiotics', 'mucoactive therapy' and 'anti-inflammatory therapy'. A keyword search on the ClinicalTrials.gov website was performed with 'bronchiectasis'. A total of 127 studies were identified, of which 21 were included.

2. Anti-infective treatment

2.1 Long-term antibiotics

There is chronic colonisation of the lower respiratory tract with bacteria in up to 70% of patients with bronchiectasis [5,10]. Up to 26% of bronchiectatic patients can be colonised with *P. aeruginosa* [10,11]. This bacterium is associated with more frequent exacerbations, poorer QofL, deteriorating lung function and increased mortality [12-14]. It has been shown that increasing bacterial load is directly proportional to an increase in the number of outpatient exacerbations and hospital admissions [5]. This in turn reduces QofL of patients – an important clinical end point in bronchiectasis. It is, therefore, considered to be important to attempt to reduce the bacterial load in the stable state with the aim of reducing exacerbations and improving QofL. One such method is the introduction of long-term antibiotics. Current antibiotics in published Phase II trials – inhaled ciprofloxacin and tobramycin – are displayed in **Table 1**.

Further Phase III studies assessing the time to next exacerbation and frequency of exacerbations are underway using inhaled ciprofloxacin. The RESPIRE study (NCT01764841) will randomise patients into one of four groups – 28 day on/28 days off ciprofloxacin dry powder for inhalation (DPI), 28 day on/28 days off placebo, 14 days on/14 days off ciprofloxacin DPI and 14 days on/14 days off placebo for 48 weeks. ORBIT-3 (NCT01515007) randomises patients to receiving dual release ciprofloxacin for inhalation once daily for 28 days on/28 days off therapy for six cycles or to placebo. These studies are currently ongoing.

In addition to the studies shown in **Table 1**, there is an open-label Phase II trial recruiting to assess the efficacy of a DPI form of tobramycin (NCT02035488). The main objective of the study is to assess the pharmacokinetics of dry powder tobramycin delivered through the 'Cyclops' inhaler device at different doses and the local tolerability. About 8 patients are to be recruited and will be given one dose of tobramycin every week. Doses will increase from 30 to 60 mg then 120 mg and finally 240 mg. Primary outcome measures include actual dose delivered.

There is another ongoing open-label trial assessing the bacterial density as the primary end point comparing combined inhaled and systemic tobramycin therapy with systemic therapy alone (NCT01677403). Patients colonised with *P. aeruginosa* will be given either saline or nebulised tobramycin 80 mg twice a day (b.i.d.) for 14 days in addition to systemic

Table 1. Long term antibiotics.

Intervention/control	Patient information	Inclusion microbiology	Primary end point	Outcome CFU/(MIC)	Other outcomes	Study
Ciprofloxacin DPI, 32.5 mg b.i.d., days 1 – 28, n = 60 Placebo, b.i.d., days 1 – 28, n = 64	N = 124. Stable for 30 days. 1 hospital admission or 2 courses of antibiotics in the past 12 months. Those on long-term antibacterial therapy were excluded	Culture positive for predefined respiratory pathogens (*P. aeruginosa*, *H. influenzae*, *S. aureus*, *S. pneumoniae*, *M. catarrhalis*, *K. pneumoniae*, *P. mirabilis*, *K. oxytoca*)	Total bacterial density in sputum after 28 days of treatment	Greater mean reduction in CFU/ml during treatment and at EOT day 28 was seen in the ciprofloxacin group $p < 0.001$. Bacterial eradication at EOT in 35% ciprofloxacin group versus 8% placebo group $p = 0.001$. 6 subjects had increased MIC levels > 4 mg/L at EOT in the ciprofloxacin arm and nil in placebo group	2 treatment emergent-serious adverse effects compared to 3 in placebo group	Wilson *et al.* [55] Randomised double-blind (2013)
Ciprofloxacin, DRCFI o.d., for 3 cycles of 28 days on/28 days off, n = 20; Placebo, o.d., for 3 cycles of 28 days on/28 days off, n = 22	N = ≥ 42 2 exacerbations in past year	Ciprofloxacin-sensitive *P. aeruginosa* at screening in sputum	Change in *P. aeruginosa* bacterial density to EOT cycle 1 (day 28)	Significant reduction in bacterial load at day 28 in DRCFI group $p < 0.001$ (modified intention-to-treat analysis). Failure to culture *P. aeruginosa* was more frequent in DRCFI group (60 vs 14%) $p = 0.003$. No significant difference in MIC levels	Prolonged time to next exacerbation (134 days vs 58) $p = 0.046$ in a modified intention-to-treat analysis. No difference between the groups at day 28 for FEV_1, QofL or 6-min walk test	Serisier *et al.* [56] Randomised double-blind (2013)
Tobramycin (nebulised), 300 mg b.i.d., 28 days, n = 37; Placebo (1.25 mg quinine sulphate), b.i.d., 28 days, n = 37	N = 74. No antibiotics within 2 weeks of screening visit	At least 10^4 CFU *P. aeruginosa* per gram of sputum	Change in *P. aeruginosa* bacterial density from baseline to week 4	Mean decrease of 4.54 $\log_{10}$ CFU/g sputum of *P. aeruginosa* in TSI arm versus a mean increase of 0.02 $\log_{10}$ CFU/g with placebo ($p < 0.01$). Tobramycin-resistant strains in 11% in TSI arm versus 3% in placebo arm ($p = 0.36$). Eradication of *P. aeruginosa* in 35% of TSI patients at week 6	Reduction in *P. aeruginosa* was a significant predictor of improved medical condition (subjective analysis: improved or not improved) throughout treatment ($p < 0.01$) and at week 6 ($p < 0.04$) in TSI arm. No difference in FEV_1 in either group but incidence of dyspnoea, wheeze and chest pain significantly greater in TSI arm ($p = 0.01$)	Barker *et al.* [57] Randomised double-blind (2000)

b.i.d.: Twice a day; DPI: Dry powder for inhalation; DRCFI: Dual release for inhalation; EOT: End of treatment; *H. influenzae*: *Haemophilus influenzae*; *K. oxytoca*: *Klebsiella oxytoca*; *K. pneumoniae*: *Klebsiella pneumoniae*; *M. catarrhalis*: *Moraxella catarrhalis*; o.d.: Once daily; *P. aeruginosa*: *Pseudomonas aeruginosa*; *P. mirabilis*: *Proteus mirabilis*; QofL: Quality of life; *S. aureus*: *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*; TSI: Tobramycin solution for inhalation.

Table 1. Long term antibiotics (continued).

Intervention/control	Patient information	Inclusion microbiology	Primary end point	Outcome CFU/(MIC)	Other outcomes	Study
Tobramycin (nebulised), 300 mg b.i.d., or placebo b.i.d., each for 6 months in a crossover fashion with a 1-month washout period in between the cycles	N = 30. An inpatient 2-week course of intravenous ceftazidime and tobramycin prior to entry	At least 3 sputum cultures in the last 6 months identified *P. aeruginosa*	No powering estimation was performed in this study. Efficacy was primarily evaluated by means of number of exacerbations, number and days of hospital admission	Significant decrease in bacterial density with tobramycin ($p = 0.038$). No change in bacterial resistance	No difference in the frequency of pulmonary exacerbations. Significant reduction in number of hospital admissions ((Mean+/- SD) 0.15+/- 0.37 in tobramycin period versus 0.75+/-1.16 in placebo group) and length of stay in tobramycin period 2.05+/- 5.03 days versus 12.65 +/- 21.8 days ($p < 0.047$). No change in FEV_1, FVC or QofL. Bronchospasm in 10% tobramycin patients (n = 3)	Drobnic *et al.* [58] Crossover double-blind (2005)
Ciprofloxacin, oral, 750 mg and tobramycin, inhaled, 300 mg/5 ml b.i.d., 14 days, n = 26. Ciprofloxacin, oral, 750 mg and placebo, 5 ml (1.25 mg quinine sulphate), b.i.d. 14 days, n = 27	N = 53. Acute exacerbation	Chronic colonisation with *P. aeruginosa*	Clinical outcome assessment at day 21 (test of cure)	Significant mean *P. aeruginosa* density reduction in the cip/tobra arm (3.67 $\log_{10}$ versus 1.15 $\log_{10}$ on day 7 and by 3.25 $\log_{10}$ versus 0.52 $\log_{10}$ on day 14 ($p < 0.001$))	No difference in clinical outcomes between the groups at day 14 or day 21 Significant increase in frequency of wheeze with 50% in cip/tobra versus 14.8% in cip/placebo ($p < 0.01$)	Bilton *et al.* [59] Randomised double-blind (2006)

b.i.d.: Twice a day; DPI: Dry powder for inhalation; DRCFI: Dual release for inhalation; EOT: End of treatment; *H. influenzae*: *Haemophilus influenzae*; *K. oxytoca*: *Klebsiella oxytoca*; *K. pneumoniae*: *Klebsiella pneumoniae*; *M. catarrhalis*: *Moraxella catarrhalis*; o.d.: Once daily; *P. aeruginosa*: *Pseudomonas aeruginosa*; *P. mirabilis*: *Proteus mirabilis*; QofL: Quality of life; *S. aureus*: *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*; TSI: Tobramycin solution for inhalation.

therapy (no additional details available). The trial is currently still recruiting and aims to enrol 120 patients.

Tobramycin has also been studied as part of a fosfomycin/tobramycin combination (4:1 w/w) drug (FTI) [15]. Results show that this could be a novel combined inhaled antibiotic for patients with bronchiectasis and CF. A Phase II study assessed the formulation's activity *in vitro* and *in vivo*. Clinical isolates from CF and bronchiectasis patients were evaluated for MIC, minimum bactericidal content, post-antibiotic effect, synergy, spontaneous mutation frequency (SMF) and time-kill in a rat pneumonia model [15]. Results showed the combination drug to have a potent dose-dependent bactericidal action against *P. aeruginosa* in the rat pneumonia model but tobramycin alone was found to be more active than the combination drug with a lower MIC_{90} (mg/L). For *P. aeruginosa* and *Staphylococcus aureus*, the SMF was lower for FTI than either of the single drugs alone. FTI had a lower MIC than either tobramycin or fosfomycin against *S. aureus* (methicillin resistance detected in 75% of strains) and a comparable MIC_{90} with vancomycin (MIC_{90} of 2 vs MIC_{90} of 1). FTI also demonstrated high activity against *S. aureus*, *Haemophilus influenzae*, *Klebsiella pneumoniae* and *Escherichia coli* but was poor against *Stenotrophomonas maltophilia* and *Burkholderia cepacia*. Synergy testing did not show any antagonism between the two drugs. Dual activity against both Gram-positive and Gram-negative bacteria makes it an attractive choice for patients colonised with multiple pathogens and may be useful in attenuating the development of drug-resistant organisms.

Another antimicrobial currently being investigated for patients with bronchiectasis is inhaled amikacin via nebuliser. A multinational Phase II trial assessing the safety and tolerability of Arikace – a liposomal form of amikacin – has been completed (NCT00775138). Patients chronically colonised with *P. aeruginosa* (n = 64) were recruited. The double-blind trial randomised patients to nebulised once-daily dosing of either 280, 560 mg of Arikace or placebo for 28 days. Co-primary end points assessed treatment-emergent adverse events and pulmonary function abnormalities. Secondary end points included time to next exacerbation, QofL and bacterial density. An interim analysis reported no concerns regarding safety and tolerability but full results have not been published yet [16].

A new antimicrobial peptide POL7080, a new class of antibiotic specific for *P. aeruginosa* infection, is currently in Phase II trials (NCT02096315). Its mechanism of action includes inactivating a bacterial target necessary for outer membrane lipopolysaccharide production. The trial aims to recruit 20 patients with bronchiectasis experiencing an acute exacerbation due to *P. aeruginosa*. Patients are given up to 14 days treatment with POL7080. The primary outcome assesses sputum bacterial clearance and secondary outcome measures include adverse effects and plasma concentrations of POL7080.

2.2 Antiviral therapy for viral exacerbations

The role of viruses in bronchiectasis exacerbations is poorly understood. The British national quality standards for bronchiectasis advise physicians to provide patients with a self-management plan to enable them to take ownership and responsibility for their condition [17]. They also advise an annual influenza vaccine and to avoid contact if possible with people known to have a viral infection to prevent viral-induced exacerbations [17]. This is based on expert consensus from clinicians managing bronchiectasis as there are no completed studies to date that investigated the role of viruses and antiviral treatment in bronchiectasis exacerbations. Studies are needed to assess the clinical efficacy of antiviral therapy in bronchiectasis exacerbations to help guide management. A Phase I study (NCT01113034) assessing the safety of antiviral agent DAS181 in patients with bronchiectasis was underway but further information regarding its current status is not available. DAS181 is a fusion protein of the sialidase catalytic domain of *Actinomyces viscosus* and the anchoring domain of the human amphiregulin. Its mechanism of action consists of cleaving the sialic acid receptor on the cells surface of host cells which influenza virus requires to infect cells [18,19]. This novel action could make it a potent inhibitor of seasonal and emerging influenza strains [20].

2.3 Preventative therapy for exacerbations

In addition to the above studies, there has been interest in immunostimulating agents. These compounds consist of antigens from several bacterial strains and are designed to stimulate an immune response. OM-85 (also known as Broncho-Vaxom) consists of extracts of eight different bacterial species (*H. influenzae*, *Streptococcus pneumoniae*, *K. pneumoniae and Klebsiella ozaenae*, *S. aureus*, *Streptococcus pyogenes*, *Streptococcus viridans* and *Neisseria catarrhalis*). It is thought to directly activate lung macrophages, enhance antigen presentation and encourage differentiation of CD4 T lymphocytes and B lymphocytes [21]. The agent has been studied in COPD and was found to significantly reduce exacerbations [22-24]. A randomised double-blind multicentre placebo-controlled trial is planned looking at the effect on exacerbations in bronchiectasis but recruitment has not yet commenced (NCT01968421).

3. Mucoactive agents

Hyperosmolar agents, sometimes referred to as 'mucoactive' therapies, are designed to enhance mucus clearance by altering its physical structure, making it less viscous and more mobile. Therapies designed to enable easier expectoration of sputum aim to break the vicious circle by preventing the infection of stagnant mucus in the lower airways.

N-acetylcysteine (NAC) has been investigated as a mucolytic therapy in COPD but to date no evidence exist in the field of bronchiectasis. NAC is thought to disrupt the mucus

gel structure by altering the degree of crosslinking or interactions between molecules in the sputum [25]. Zheng *et al.* conducted a randomised trial and proposed a 600 mg b.i.d. regime could reduce the rate of exacerbations in moderate and severe COPD patients [26]. Although further work is needed before it is incorporated into clinical practice [27], the potential for NAC to be used in other respiratory conditions like bronchiectasis should be considered. A randomised control trial is currently ongoing where the researchers aim to recruit 120 bronchiectasis patients to either NAC 600 mg b.i.d. for 12 months or placebo (NCT02088216). The primary end point examines exacerbations of bronchiectasis.

4. Anti-inflammatory agents

The inflammation caused by persistent bacterial infection and colonisation further propagates the vicious circle. This part of the circle naturally lends itself to being targeted by anti-inflammatory therapies.

Statins have been used in cardiovascular medicine to lower cholesterol and have also been associated with reduced mortality rates in patients with influenza virus [28]. Their pleiotropic effects, in particular, their anti-inflammatory properties have made them a potential therapeutic agent in bronchiectasis. Of note, there is reduced neutrophil inflammation in healthy volunteer studies exposed to lipopolysaccharide [29]. Mandal *et al.* recently published a randomised controlled trial of high-dose atorvastatin (80 mg) versus placebo in bronchiectasis (**Table 2**) [30]. The same group have gone on to assess the use of atorvastatin in patients with *P. aeruginosa* in a crossover trial assessing cough as the primary end point (NCT01299194). Patients will receive 80 mg atorvastatin or placebo for 3 months followed by a 6-week wash-out period. They will then crossover to the other arm for a further 3 months. The study will also assess the effect on cough. This trial has completed recruitment but results have not yet been published.

Theophylline forms part of the stepwise treatment for asthma as outlined in the NICE guidelines [31,32]. The mechanism of action of theophylline is not fully understood but it is thought to have some anti-inflammatory effects by inhibiting phosphodiesterase (inhibits TNF-α, inhibits leukotriene synthesis, reduces inflammation and innate immunity) in addition to antagonising adenosine receptors and inhibiting TGF-β-mediated conversion of pulmonary fibroblasts. Theophylline may be useful in patients with steroid resistance as it is able to restore histone deacetylase levels and enhance the anti-inflammatory effects of steroids [33]. There have not yet been any large trials in bronchiectasis but there are two small randomised parallel studies currently recruiting patients in bronchiectasis. The first study assesses the safety and efficacy of 24 weeks of theophylline 100 mg b.i.d. against placebo (NCT01684683). A further randomised study investigating the role of theophylline with low dose formoterol–budesonide over a 24-week period is also recruiting for patients with bronchiectasis (NCT01769898). The primary outcome for both studies assesses QofL as measured by the St George's Respiratory Questionnaire. Similarly, roflumilast – a phosphodiesterase type-4 inhibitor – has shown some efficacy in reducing neutrophilic inflammation in COPD patients but has not yet been studied in bronchiectasis [34]. Roflumilast has been licensed in COPD and could be a potential anti-inflammatory agent in bronchiectasis but randomised controlled trials are required first. A Phase II study is planned in symptomatic bronchiectasis patients but status information regarding this trial is not available (NCT01580748).

NSAIDS have been investigated for their anti-inflammatory effects in bronchiectasis (**Table 2**). The mechanism of action in the study by Llewellyn-Jones *et al*. showed reduced resident neutrophil chemotaxis and therefore this agent may be useful in bronchiectasis by reducing airway neutrophil inflammation [35].

Neutrophil elastase inhibitors are thought to have potential in reducing the inflammatory response seen in the airways of patients with bronchiectasis. In bronchiectasis, there is excess neutrophilic airway inflammation and free elastase is found in patients with more advanced bronchiectasis. Neutrophil elastase inhibition offers a potential therapeutic intervention. To date, there has been one completed Phase II trial investigating the compound AZD9668 – an oral neutrophil elastase inhibitor (**Table 2**) [36]. A further Phase II trial (NCT01818544) assessing BAY85-8501, a neutrophil elastase inhibitor, has just completed but results are awaited. The primary outcome of this study is to assess the safety and tolerability of 28 days oral administration of BAY85-8501 versus placebo.

The generation of oxygen-free radicals is a part of the neutrophilic inflammatory response and is known to damage airways. It has, therefore, been postulated that the imbalance between oxidants and antioxidants may play a role in bronchiectasis. To investigate this further Cobanoglu *et al*. explored the effect of β-carotene in children with CF, bronchiectasis and healthy controls (**Table 2**) [37].

Novel treatments are being sought to break the 'vicious circle' of bronchiectasis and some of the newer agents include AZD5069 (CXC chemokine receptor 2 antagonist CXCR2). Its mechanism of action includes reducing calcium flux and chemotactic response to known chemoattractants. AZD5069 had undergone Phase I studies to understand its safety and efficacy (NCT00953888) and the change in its pharmacokinetic profile when co-administered to healthy volunteers with ketoconazole (NCT01735240). A subsequent Phase II study (NCT01255592) enrolled 83 bronchiectasis patients in a randomised placebo-controlled trial to receive either AZD5069 b.i.d. for 28 days or placebo. The trial has concluded but results have not yet been published.

5. Conclusion

The vicious circle of bronchiectasis needs to be broken in order to improve symptoms, prevent recurrent infections

Table 2. Anti-inflammatory therapies.

Intervention/control	Patient information	Inclusion microbiology	Primary outcome	Outcome CFU/ (MIC)	Other outcomes	Study
Atorvastatin, 80 mg, o.d. for 6 months, n = 30; Placebo, o.d. for 6 months, n = 30	Clinically significant bronchiectasis 2 or more chest infections in preceding year. Smokers > 15-year pack history, ex-smokers of < 1 year were all excluded	Patients with chronic colonisation with *P. aeruginosa* were excluded	Reduction in cough from baseline to 6 months, as measured by the LCQ	Chronic colonisation increase from 57 to 63% with atorvastatin. Chronic colonisation remained at 40% in placebo group. No significant difference in bacterial load at 6 months in either group	Significant improvement in cough (p = 0.01) in the atorvastatin group. 33% in atorvastatin group had an adverse event versus 10% in placebo group (p = 0.02). FEV_1 and FVC remained unchanged. Exercise capacity improved by 35 m in the atorvastatin group. Serum IL-8 and CRP fell from baseline levels with atorvastatin. 8/24 had ≥ 2 exacerbations and 5/24 had ≥ 3 exacerbations with atorvastatin group versus 16/29 and 10/29 in placebo group, respectively	Mandal *et al.* [30] Randomised control trial (2014)
Indomethacin, 2 ml of aerosolised preparation containing 1.2μg/ml t.i.d., 14 days, n = 13; Placebo, t.i.d., 14 days, n = 12	N = 25 Bronchorrhoea for 4 weeks prior to study. Chronic bronchitis, (12) diffuse panbronchiolitis (5) and bronchiectasis (8)	(17) *P. aeruginosa*, (3) *H. influenzae*, (1) *S. aureus*	Primary end point not specified in paper	No change in total bacterial CFU/g or in bacterial flora in either group	No significant difference in FEV_1 or FVC in either group. Breathlessness assessed by Borg's score improved with indomethacin only (from 7.1 ± 0.5 to 4.5 ± 0.4, p < 0.01). 2 patients in the indomethacin group developed dry mouth but hypotension or bronchoconstriction was not observed. Sputum weight significantly reduced from 189 ± 19 to 95 ± 21 g/day at day 14 in the indomethacin group (p < 0.001)	Tamaoki *et al.* [60] Randomised controlled trial (1992)
Indomethacin, 25 mg, t.i.d., 28 days, n = 9; Indomethacin, 25 mg, t.i.d., 14 days, n = 8	N = 9 clinically stable bronchiectasis. No inhaled or oral steroids in past 3 months; N = 8 healthy volunteers	(7) *H. influenzae*, (5) *B. catarrhalis*, (3) *S. pneumoniae*, (1) *P. aeruginosa*, (1) *P. mirabilis* from the 9 bronchiectasis patients (patients grew more than 1 organism)	Primary end point not specified in paper (lab-based study)	No significant difference in total sputum bacterial load, no change in 12-h sputum volume in sputum	No adverse effects recorded, no change in sputum characteristics or peak flow recorded and no exacerbations during treatment. Significant reduction in peripheral neutrophil chemotaxis to 10 nmol/L FMLP (p < 0.0001) at day 28, returning to baseline at day 63.	Llewellyn-jones *et al.* [35] Open-labelled (1995)

BC: *Branhamella catarrhalis*; BE: Bronchiectasis; b.i.d.: Twice a day; CF: Cystic fibrosis; CFU: Colony forming unit; CRP: C-reactive protein; FMLP: *N*-formyl-methionyl-leucyl-phenylalanine; *H. influenzae*: *Haemophilus influenzae*; *K. pneumoniae*: *Klebsiella pneumoniae*; LCQ: Leicester Cough Questionnaire; *M. catarrhalis*: *Moraxella catarrhalis*; MDA: Malondialdehyde; o.d.: Once daily; *P. aeruginosa*: *Pseudomonas aeruginosa*; QofL: Quality of life; *S. aureus*: *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*; *P. mirabilis*: *Proteus mirabilis*; t.i.d.: Three times a day; VE: Vitamin E.

Table 2. Anti-inflammatory therapies (continued).

Intervention/control	Patient information	Inclusion microbiology	Primary outcome	Outcome CFU/ (MIC)	Other outcomes	Study
					Significant reduction in fibronectin degradation by resting and stimulated neutrophils in bronchiectasis patients at day 14 and day 28, returning back to baseline at day 63 ($p < 0.001$). Similar neutrophil results in healthy controls after 14-day treatment. No change in superoxide generation, intracellular elastase or myeloperoxidase in bronchiectasis samples	
AZD9668, 60 mg, b.i.d., 4 weeks, n = 22; Placebo, b.i.d., n = 16	Idiopathic or post-infective bronchiectasis. Clinically stable for 6 weeks prior to entry into study	9 with non-*Pseudomonas* organisms, 9 with *Pseudomonas* in AZD9668 group	No powering estimation was performed for this study	No information supplied	Significant changes defined *a priori* as $p < 0.1$. No change in sputum neutrophils with AZD9668. FEV_1 improved by 100 ml ($p = 0.006$) and slow vital capacity improved by 130 ml ($p = 0.079$) with AZD9668. Plasma IL-8 reduced with AZD9668 ($p = 0.085$). Post-waking sputum IL-6 reduced with AZD9668 ($p = 0.098$). No significant difference in QofL, sputum weight or other lung function parameters. AZD9668 was well tolerated with commonest side effect of headache (7/22 in AZD9668 vs 2/16 in placebo group)	Stockley *et al.* [36] Randomised control trial (2013)

BC: *Branhamella catarrhalis*; BE: Bronchiectasis; b.i.d.: Twice a day; CF: Cystic fibrosis; CFU: Colony forming unit; CRP: C-reactive protein; FMLP: *N*-formyl-methionyl-leucyl-phenylalanine; *H. influenzae*: *Haemophilus influenzae*; *K. pneumoniae*: *Klebsiella pneumoniae*; LCQ: Leicester Cough Questionnaire; *M. catarrhalis*: *Moraxella catarrhalis*; MDA: Malondialdehyde; o.d.: Once daily; *P. aeruginosa*: *Pseudomonas aeruginosa*; QofL: Quality of life; *S. aureus*: *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*; *P. mirabilis*: *Proteus mirabilis*; t.i.d.: Three times a day; VE: Vitamin E.

Table 2. Anti-inflammatory therapies (continued).

Intervention/control	Patient information	Inclusion microbiology	Primary outcome	Outcome CFU/ (MIC)	Other outcomes	Study
β-carotene, oral, 0.69 ± 0.19 mg kg^{-1} t.i.d. with meals for CF and bronchiectasis patients only, 6 months	CF n = 18, BE n = 15, healthy children n = 15. Conditions where reactive oxygen species have been implicated were excluded (cirrhosis, hepatitis, diabetes mellitus, corticosteroid therapy or insulin therapy)	Not specified	No primary end point specified, explorative study	Not specified	VE levels were significantly lower than healthy volunteers at baseline with CF (p = 0.001) and BE (p = 0.0001). β-carotene levels were significantly lower in CF group than healthy volunteers at baseline (p = 0.008) CF and BE has significantly higher MDA (biomarker of lipid peroxidation due to free radical oxidation) than healthy controls at baseline (p = 0.0001). Post-treatment VE and BC increased in both CF (p = 0.007, p = 0.001) and BE (p = 0.008, p = 0.001). Post-treatment reduction in TNF-α and MDA in both CF (p = 0.022, p = 0.001) and BE (p = 0.035, p = 0.015). Post-treatment vital capacity improved in BE (p = 0.02), FEV_1 and FEV_{25-75} improved in CF (p = 0.016, p = 0.017 respectively)	Cobanoglu *et al.* [37] Open-labelled (2002)

BC: *Branhamella catarrhalis*; BE: Bronchiectasis; b.i.d.: Twice a day; CF: Cystic fibrosis; CFU: Colony forming unit; CRP: C-reactive protein; FMLP: *N*-formyl-methionyl-leucyl-phenylalanine; *H. influenzae*: *Haemophilus influenzae*; *K. pneumoniae*: *Klebsiella pneumoniae*; LCQ: Leicester Cough Questionnaire; *M. catarrhalis*: *Moraxella catarrhalis*; MDA: Malondialdehyde; o.d.: Once daily; *P. aeruginosa*: *Pseudomonas aeruginosa*; QofL: Quality of life; *S. aureus*: *Staphylococcus aureus*; *S. pneumoniae*: *Streptococcus pneumoniae*; *P. mirabilis*: *Proteus mirabilis*; t.i.d.: Three times a day; VE: Vitamin E.

and halt any potential progression of the disease. A number of new therapies are in the pipeline targeting not only the bacterial burden in the lower airways but also the excessive neutrophilic inflammatory response seen in patients with bronchiectasis. Ultimately Phase III trials are needed before these agents can become licensed for routine use in bronchiectasis.

6. Expert opinion

Bronchiectasis was first described over a century ago and despite this there is a lack of large randomised controlled trials compared to other chronic respiratory conditions. The heterogeneity of this condition and associated co-morbidities makes managing this condition challenging. We have focused the review on idiopathic and post-infective bronchiectasis, the commonest aetiologies found in bronchiectasis, which in our opinion is managed similarly. The aims of treatment of patients with clinically significant bronchiectasis are to reduce cough, sputum volume, sputum purulence, number of exacerbations and to improve QofL.

The management of bronchiectasis should be based on the clinical impact for each individual patient. For patients with mild disease, treatment should be focused on prevention of exacerbations. This includes daily chest clearance using the active cycle breathing technique or alternatives recommended by the respiratory physiotherapist, if unable to carry out the active cycle breathing technique. For younger patients, we would recommend positive expiratory pressure devices such as the Acapella®. We would recommend an annual influenza vaccination and the pneumococcal vaccination every 5 years. The conjugate pneumococcal vaccine in our opinion offers potential immunological therapeutic advantages over the traditional polysaccharide vaccine but requires further study. Immunostimulating agents are an exciting future therapeutic strategy but further studies are needed before this can be implemented into clinical practice. This group of patients have limited exacerbations, and exacerbations should be treated promptly with antibiotics as per sputum culture and sensitivities. In our opinion, there is no need in this group to receive mucoactive therapies or long-term anti-inflammatory or anti-infective therapies.

In our view, therapy for moderate clinical disease therapy should be targeted at improving symptoms and preventing disease progression. In our opinion, these patients may benefit from mucoactive therapies. The strongest evidence exists for hypertonic saline [38-40] and mannitol [41-46] which increase sputum expectoration and promote airway clearance. We would recommend using hypertonic saline (7%) in patients who have difficulty in achieving airway clearance with active cycle breathing technique alone. We would recommend reserving the use of inhaled mannitol until the results are available from Phase III studies.

Anti-inflammatory agents are an exciting therapeutic option which may improve symptoms and prevent disease progression. Recently, we have seen the publication of large trials assessing the use of macrolides as a potential anti-inflammatory therapy to reduce exacerbation frequency [47-49]. We believe that the side-effect profile of macrolides in this group of patients outweighs the potential therapeutic advantages of reducing exacerbations. The side-effect profile we are concerned with are the increased pneumococcal resistance to macrolides, the adverse effects on hearing and balance, the gastrointestinal side effects and the potential risk of macrolide-resistant non-tuberculosis mycobacteria. In patients with bronchiectasis there is excess neutrophil airway inflammation with free elastase activity and high levels of chemoattractants such as IL-8, leukotriene B4 and Complement 5A in the airways. Our view is that the neutrophil elastase inhibitors, CXCR2 antagonists and statins are the most promising therapeutic agents as they target the neutrophil airway inflammation. The best evidence exists for statins as they have been shown in a preliminary study to improve neutrophil apoptosis and reduce cough but is not currently sufficient to put into routine clinical practice [30]. The benefit of statins over macrolides is that it not being an antibiotic and, therefore, if it can be tolerated, it is a safer long-term strategy. Ultimately, larger randomised controlled trials are needed. In our practice, anti-inflammatory therapies are not currently used for this group but probably should be in the future when more evidence exists.

For severe bronchiectasis, we would recommend long-term antibiotics. The rationale for long-term antibiotic treatment is to reduce bacterial burden in the airways. Consequently this would reduce the number of exacerbations and improve QofL. This was shown in the 12-month Phase III trial of nebulised gentamicin [50]. The study showed gentamicin was efficacious in reducing the number of exacerbations, in improving QofL, in increasing time to next exacerbation, in reducing sputum volume, in reducing sputum purulence and in reducing bacterial load but reported all markers returned to baseline after 3 months off treatment [50]. The study by Haworth *et al.* [51] showed that nebulised colomycin continuously for 6 months reduced time to next exacerbation only if patients complied with therapy. Studies to date using cyclical therapy (using inhaled aztreonam) on and off have failed to show clinical benefit [52]. In our opinion, inhaled antibiotics should be used in patients chronically infected with *P. aeruginosa* with three or more exacerbations per year. In fully sensitive *P. aeruginosa*, we would use nebulised gentamicin as first line in view of its proven efficacy and low cost. As second line we would use colomycin and third line tobramycin. We use these agents continuously for life but monitor the gentamicin levels in serum, hearing and renal function and sputum sensitivities.

We use long-term oral therapy for patients with severe bronchiectasis (three or more exacerbations per year) and chronic infection with other potential pathogenic organisms except *P. aeruginosa*. The commonest pathogen is *H. influenzae*, and we treat with long-term amoxicillin if it is a

β-lactamase-negative-producing organism. We treat these patients long term but monitor side effects, sputum culture and sensitivities and adjust long-term treatments as required.

If there is failure despite this treatment, we would consider long-term anti-inflammatory treatment in addition. We would use long-term azithromycin in view that the long-term benefits outweigh the disadvantages in this group of patients. We, however, send three sputum samples for mycobacterial culture first and only use in patients with no evidence of non-tuberculosis mycobacteria. This treatment would be continued long term as long as there were no side effects that require treatment cessation. We would use macrolides before other potential anti-inflammatory therapies in view that these are the only treatments that have been shown to be of benefit in international trials.

We reserve regular intravenous antibiotics, administered in 8 weekly cycles, for those patients unresponsive or intolerant to the above therapies and have five or more exacerbations per year. The only study to date on regular intravenous therapy reported that patients feel better and required less antibiotic therapy overall [53].

Originally a lot of therapies were based on those used for CF but we have learnt a lot from the inhaled DNase study [54] that treatments that work in CF can be harmful in non-CF bronchiectasis. In the next five years we hope to see multiple Phase III clinical trials using different inhaled antibiotic therapies and multiple Phase II trials assessing anti-inflammatory therapies, leading to further Phase III trials, so these treatments can become licensed for patients with bronchiectasis. The ultimate challenge will be to decide when we should institute both anti-inflammatory and anti-infective therapies and in which patients. In our opinion if we target people earlier with moderate disease we will hopefully improve symptoms and halt disease progression. This review has focussed on chronic management but another challenge is defining exacerbations and investigating how they should be treated. Currently, we treat with oral antibiotics as first line and if this fails proceed to intravenous antibiotics using therapies based on sputum cultures and sensitivity patterns for 14 days. There are ongoing studies addressing optimal length of therapy (NCT02047773) which is another fertile area for future research.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organisation or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents, received or pending, or royalties.

Bibliography

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Pasteur MC, Bilton D, Hill AT. British Thoracic Society guideline for non-CF bronchiectasis. Thorax 2010(65 Suppl 1):i1-58

•• **International guidelines on bronchiectasis.**

2. Bilton D, Jones AL. Chapter 1: bronchiectasis: epidemiology and causes. In: Floto RA, Haworth CS, editors. Bronchiectasis. European Respiratory Society; Lausanne, Switzerland: 2011. Published online May 26, 2011; doi:10.1183/1025448x.10003110

3. Weycker D, Edelsberg J, Oster G, et al. Prevalence and economic burden of bronchiectasis. Clin Pulm Med 2005;12(4):205-9

4. Reid LM. Reduction in bronchial subdivision in bronchiectasis. Thorax 1950;5(3):233-47

5. Chalmers JD, Smith MP, McHugh BJ, et al. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2012;186(7):657-65

•• **A key study exploring the mechanisms and importance of bacterial infection and bacterial load in bronchiectasis.**

6. O'Donnell AE. Bronchiectasis. CHEST J 2008;134(4):815-23

7. Kelly MG, Murphy S, Elborn JS. Bronchiectasis in secondary care: a comprehensive profile of a neglected disease. Eur J Intern Med 2003;14(8):488-92

8. Nicotra MB, Rivera M, Dale AM, et al. Clinical, pathophysiologic, and microbiologic characterization of bronchiectasis in an aging cohort. Chest 1995;108(4):955-61

9. Cole P. Host-microbe relationships in chronic respiratory infection. Respiration 1989(55 Suppl 1):5-8

• **First description of the vicious circle of bronchiectasis.**

10. Angrill J, Agusti C, de Celis R, et al. Bacterial colonisation in patients with bronchiectasis: microbiological pattern and risk factors. Thorax 2002;57(1):15-19

• **A study describing the microbial flora in bronchiectasis.**

11. Hill AT, Welham S, Reid K, Bucknall CE. British thoracic society national bronchiectasis audit 2010 and 2011. Thorax 2012;67:928-30

12. Wilson CB, Jones PW, O'Leary CJ, et al. Effect of sputum bacteriology on the quality of life of patients with bronchiectasis. Eur Respir J 1997;10(8):1754-60

•• **Paper describing the effect of bacterial infection in bronchiectasis.**

13. Martinez-Garcia MA, Soler-Cataluna JJ, Perpina-Tordera M, et al. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. Chest 2007;132(5):1565-72

•• **Reasons for decline in FEV_1 in bronchiectasis.**

14. Evans SA, Turner SM, Bosch BJ, et al. Lung function in bronchiectasis: the

influence of Pseudomonas aeruginosa. Eur Respir J 1996;9(8):1601-4

•• ***Pseudomonas aeruginosa* leads to accelerated decline in bronchiecatsis.**

15. MacLeod DL, Barker LM, Sutherland JL, et al. Antibacterial activities of a fosfomycin/tobramycin combination: a novel inhaled antibiotic for bronchiectasis. J Antimicrob Chemother 2009;64(4):829-36

16. O'Donnell AE, Swarnakar R, Yahina L, et al. A placebo-controlled study of liposomal amikacin for inhalation nebulized once daily in the treatment of bronchiectatic patients with chronic Pseudomonas aeruginosa lung infection. Eur Respir J 2009;34:231S

17. Hill A, Bilton D, Brown J, et al. British thoracic society quality standards for clinically significant bronchiectasis in adults July 2012. Br Thorac Soc Rep 2012;4:1-16

•• **First quality standards created for bronchiecatsis.**

18. Malakhov MP, Aschenbrenner LM, Smee DF, et al. Sialidase fusion protein as a novel broad-spectrum inhibitor of influenza virus infection. Antimicrob Agents Chemother 2006;50:1470-9

19. Nicholls JM, Aschenbrenner LM, Paulson JC, et al. Comment on: concerns of using sialidase fusion protein as an experimental drug to combat seasonal and pandemic influenza. J Antimicrob Chemother 2008;62:426-8

20. Triana-Baltzer GB, Gubareva LV, Nicholls JM, et al. Novel pandemic influenza A(H1N1) viruses are potently inhibited by DAS181; a sialidase fusion protein. PLoS One 2009;4(11):e7788

21. Emmerich B, Emslander HP, Pachmann K, et al. Local immunity in patients with chronic bronchitis and the effects of a bacterial extract, Bronco-AvxomR, on T-lymphocytes, macrophages, gamma-interferon and secretory immunoglobulin A in bronchoalveolar lavage fluid and other variables. Respiration 1990;57:90-9

22. Collet JP, Shapiro P, Ernst P, et al. Effects of an immunostimulating agent on acute exacerbations and hospitalizations in patients with chronic obstructive pulmonary disease. The PARI-IS Study Steering Committee and Research Group. Prevention of Acute Respiratory Infection by an Immunostimulant. Am J Respir Crit Care Med 1997;156(6):1719-24

23. Orcel B, Delclaux B, Baud M, et al. Oral immunization with bacterial extracts for protection against acute bronchitis in elderly institutionalized patients with chronic bronchitis. Eur Respir J 1994;7(3):446-52

24. Soler M, Mutterlein R, Cozma G. Double-blind study of OM-85 in patients with chronic bronchitis or mild chronic obstructive pulmonary disease. Respiration 2007;74(1):26-32

25. Sadowska A, Verbraecken J, Darquennes K, De Backer WA. Role of N-acetylcysteine in the management of COPD. Int J Chron Obstruct Pulmon Dis 2006;1(4):425-34

26. Zheng JP, Wen FQ, Bai CX, et al. Twice daily N-acetylcysteine 600 mg for exacerbations of chronic obstructive pulmonary disease (PANTHEON): a randomised, double-blind placebo-controlled trial. Lancet Respir Med 2014;2(3):187-94

27. Turner RD, Bothamley GH. N-acetylcysteine for COPD: the evidence remains inconclusive. Lancet Respir Med 2014;2(4):e3

28. Vandermeer ML, Thomas AR, Kamimoto L, et al. Association between use of statins and mortality among patients hospitalized with laboratory-confirmed influenza virus infections: a multistate study. J Infect Dis 2012;205(1):13-19

29. Shyamsundar M, McKeown ST, O'Kane CM, et al. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. Am J Respir Crit Care Med 2009;179(12):1107-14

30. Mandal P, Chalmers JD, Graham C, et al. Atorvastatin as a stable treatment in bronchiectasis: a randomised controlled trial. Lancet Respir Med 2014;2(6):455-63

•• **A randomised control trial of statins in bronchiectasis.**

31. www.nice.org.uk/asthma

32. Clinical trial of low-dose theophylline and montelukast in patients with poorly controlled asthma. Am J Respir Crit Care Med 2007;175(3):235-42

33. Ito K, Lim S, Caramori G, et al. A molecular mechanism of action of theophylline: induction of histone deacetylase activity to decrease inflammatory gene expression. Proc Natl Acad Sci USA 2002;99(13):8921-6

34. Milara J, Lluch J, Almudever P, et al. Roflumilast N-oxide reverses corticosteroid resistance in neutrophils from patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol 2014;134(2):314-22

35. Llewellyn-Jones CG, Johnson MM, Mitchell JL, et al. In vivo study of indomethacin in bronchiectasis: effect on neutrophil function and lung secretion. Eur Respir J 1995;8(9):1479-87

• **NSAIDS in bronchiecatsis.**

36. Stockley R, De Soyza A, Gunawardena K, et al. Phase II study of a neutrophil elastase inhibitor (AZD9668) in patients with bronchiectasis. Respir Med 2013;107(4):524-33

• **Elastase inhibitors in bronchiectasis.**

37. Cobanoglu N, Ozcelik U, Gocmen A, et al. Antioxidant effect of beta-carotene in cystic fibrosis and bronchiectasis: clinical and laboratory parameters of a pilot study. Acta Paediatrica 2002;91(7):793-8

38. Kellett F, Redfern J, Niven RM. Evaluation of nebulised hypertonic saline (7%) as an adjunct to physiotherapy in patients with stable bronchiectasis. Respir Med 2005;99(1):27-31

• **Important study on hypertonic saline in bronchiectasis.**

39. Kellett F, Robert NM. Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respir Med 2011;105(12):1831-5

• **Important study on hypertonic saline in bronchiectasis.**

40. Nicolson CH, Stirling RG, Borg BM, et al. The long term effect of inhaled hypertonic saline 6% in non-cystic fibrosis bronchiectasis. Respir Med 2012;106(5):661-7

• **Important study on hypertonic saline in bronchiectasis.**

41. Daviskas E, Anderson SD, Gomes K, et al. Inhaled mannitol for the treatment of mucociliary dysfunction in patients with bronchiectasis: effect on lung function, health status and sputum. Respirology (Carlton, Vic) 2005;10(1):46-56

• **Important study on mannitol in bronchiectasis.**

42. Daviskas E, Anderson SD, Eberl S, et al. Effect of increasing doses of mannitol on mucus clearance in patients with bronchiectasis. Eur Respir J 2008;31(4):765-72
• **Important study on mannitol in bronchiectasis.**

43. Bilton D, Daviskas E, Anderson SD, et al. Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-cystic fibrosis bronchiectasis. Chest 2013;144(1):215-25
•• **Important Phase III study on manniol in bronchiectasis.**

44. Daviskas E, Anderson SD, Eberl S, et al. Inhalation of dry powder mannitol improves clearance of mucus in patients with bronchiectasis. Am J Respir Crit Care Med 1999;159(6):1843-8
• **Important study on mannitol in bronchiectasis.**

45. Daviskas E, Anderson SD, Gomes K. Increase in health status after 12 days treatment with inhaled mannitol in patients with bronchiectasis. Eur Respir J 2003;22:Suppl 45:p. 430
• **Important study on mannitol in bronchiectasis.**

46. Daviskas E, Anderson SD, Eberl S, et al. The 24-h effect of mannitol on the clearance of mucus in patients with bronchiectasis. Chest 2001;119(2):414-21
• **Important study on mannitol in bronchiectasis.**

47. Wong C, Jayaram L, Karalus N, et al. Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet 2012;380(9842):660-7
•• **Randomised controlled trial of macrolide use in bronchiectasis.**

48. Serisier DJ, Martin ML, McGuckin MA, et al. Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA 2013;309(12):1260-7
•• **Randomised controlled trial of macrolide use in bronchiectasis.**

49. Altenburg J, de Graaff CS, Stienstra Y, et al. Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 2013;309(12):1251-9
•• **Randomised controlled trial of macrolide use in bronchiectasis.**

50. Murray MP, Govan JR, Doherty CJ, et al. A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2011;183(4):491-9
•• **Long-term use of nebulised gentamicin in bronchiectasis.**

51. Haworth CS, Foweraker JE, Wilkinson P, et al. Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. Am J Respir Crit Care Med 2014;189(8):975-82
•• **Important study on inhaled antibiotics in bronchiectasis.**

52. Barker AF, O'Donnell AE, Flume P, et al. Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. Lancet Respir Med 2014;2(9):738-49

53. Mandal P, Sidhu MK, Donaldson LS, et al. Eight-weekly intravenous antibiotics is beneficial in severe bronchiectasis. QJM 2013;106(1):27-33

54. O'Donnell AE, Barker AF, Ilowite JS, Fick RB. Treatment of idiopathic bronchiectasis with aerosolized recombinant human dnase. Chest 1998;113:1329-34

55. Wilson R, Welte T, Polverino E, et al. Ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis: a phase II randomised study. Eur Respir J 2013;41(5):1107-15
•• **Important study on inhaled antibiotics in bronchiectasis.**

56. Serisier DJ, Bilton D, De Soyza A, et al. Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis (ORBIT-2): a randomised, double-blind, placebo-controlled trial. Thorax 2013;68(9):812-17
•• **Important study on inhaled antibiotics in bronchiectasis.**

57. Barker AF, Couch L, Fiel SB, et al. Tobramycin solution for inhalation reduces sputum Pseudomonas aeruginosa density in bronchiectasis. Am J Respir Crit Care Med 2000;162(2 Pt 1):481-5
•• **Important study on inhaled antibiotics in bronchiectasis.**

58. Drobnic ME, Sune P, Montoro JB, et al. Inhaled tobramycin in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection with Pseudomonas aeruginosa. Ann Pharmacother 2005;39(1):39-44
•• **Important study on inhaled antibiotics in bronchiectasis.**

59. Bilton D, Henig N, Morrissey B, et al. Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of Pseudomonas aeruginosa infection in adult bronchiectasis. Chest 2006;130(5):1503-10
•• **Important study on inhaled antibiotics in bronchiectasis.**

60. Tamaoki J, Chiyotani A, Kobayashi K, et al. Effect of indomethacin on bronchorrhea in patients with chronic bronchitis, diffuse panbronchiolitis, or bronchiectasis. Am Rev Respir Dis 1992;145(3):548-52

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