Antibiotic Management in Bronchiectasis

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KEYWORDS

• Bronchiectasis • Antibiotics • Intravenous • Nebulized • Oral • Exacerbation • Chronic suppressive • Eradication

KEY POINTS

- Antibiotics are commonly prescribed as treatment of pulmonary exacerbations, as maintenance therapy in the context of a high exacerbation frequency or a history of severe exacerbation, and for eradication of significant pathogens.
- Antibiotic prescribing decisions must take in to account the potential for treatment-related side effects and the development of antibiotic resistance.
- Pivotal phase III studies evaluating the impact of inhaled antibiotics on exacerbation frequency are ongoing.

INTRODUCTION

Bronchiectasis is a condition characterized by irreversible dilatation of the airways[1] resulting from changes in the elastic and muscular components of the bronchial wall. The Cole vicious circle hypothesis for the pathogenesis of bronchiectasis[2] proposed that an initial insult results in a cycle of bronchial wall inflammation and damage, disordered mucociliary clearance, a predisposition to chronic or recurrent infection, and consequently further airway damage. The model allows for different etiologies of bronchiectasis to enter the cycle at different stages, and this concept was updated by Flume and colleagues[3] who suggested that each pathophysiological step likely contributes to all others, describing a vortex of interrelated pathways. Although antibiotics are undoubtably a key intervention in the management of patients with bronchiectasis (through eradicating or suppressing airway infection and inflammation), the vortex concept suggests that antibiotic treatment alone is unlikely to halt the myriad of pathophysiological processes contributing to airway wall damage. Instead, clinical outcomes may only be optimized through a multimodality approach involving not only anti-infective therapies but also mucoactive compounds and anti-inflammatory agents.

There are 3 main indications for antibiotic use in patients with bronchiectasis: (1) management of pulmonary exacerbations, (2) maintenance therapy, and (3) eradication of newly acquired pathogens.

ANTIBIOTIC TREATMENT OF PULMONARY EXACERBATIONS

A pulmonary exacerbation of bronchiectasis has recently been defined by an international consensus committee as a deterioration in 3 or more key signs and symptoms (cough, sputum volume and/or consistency, sputum purulence, breathlessness and/or exercise tolerance, fatigue and/or malaise, and hemoptysis) for at least 48 hours that a clinician determines requires a change in treatment.[4] Patients also may complain of chest tightness, wheeze, chest discomfort, night sweats, and temperatures. Symptoms usually progress over days, but patients can

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experience a more insidious decline over weeks or months.

The treatment of pulmonary exacerbations with antibiotics has largely been informed by clinical experience, because there have been no randomized placebo-controlled trials evaluating this intervention. Antibiotics are known to lead to symptom resolution as well as reduce sputum volume, sputum purulence and sputum bacterial density, C-reactive protein, and sputum inflammatory markers.[5–11]

Published data on the treatment of exacerbations with antibiotics are extremely heterogeneous in terms of the class of antibiotic evaluated, the route of administration used, and the baseline sputum microbiology of the participants. Nevertheless, certain management principles can be derived from these studies: (1) higher-dose antibiotics are generally more effective than lower-dose treatment[5]; (2) individuals with purulent as opposed to mucoid sputum following antibiotic treatment have a shorter time to next exacerbation[5]; (3) drug susceptibility test results do not necessarily predict clinical response to treatment[12]; (4) short courses of oral antibiotics prescribed for exacerbations reduce markers of airway inflammation, but chronic low grade inflammation remains[6]; and (5) clinical response may not be associated with significant improvements in spirometry.[9,10,13]

Oral antibiotics are usually prescribed as first-line treatment for a pulmonary exacerbation, except when the patient displays severe symptoms and/or signs that warrant intravenous treatment. The most appropriate dose and duration of antibiotic treatment also should be determined by the severity of the exacerbation. However, clinical experience suggests that better outcomes are generally seen with higher-dose, longer-duration regimens, probably because of the difficulty of achieving adequate concentrations of antibiotic within the lumen of bronchiectatic airways, particularly in the context of chronic infection where bacteria are often protected by biofilms. The European Respiratory Society guidelines suggest that acute exacerbations of bronchiectasis should be treated with 14 days of antibiotics[14]; however, this was a conditional recommendation, reflecting the paucity of trial data to inform management. It was also acknowledged that shorter duration treatment may be appropriate in the context of mild symptoms, mild bronchiectasis disease severity, drug-susceptible organisms, or a rapid initial response to treatment. Ideally, a sputum culture should be sent before starting empiric antibiotic treatment so that the results can inform treatment changes if the clinical response is suboptimal.

Oral Antibiotic Treatment for Pulmonary Exacerbations

Oral antibiotic treatment should be guided, where possible, by historic sputum culture results; suggestions for treatment are outlined in **Table 1**.[15] Empiric treatment may be with amoxicillin 500 mg to 1 g 3 times daily, or co-amoxiclav 625 mg 3 times daily for patients in whom beta-lactamase–producing organisms are suspected. Doxycycline 100 mg twice daily is an alternative choice in the context of penicillin allergy and ciprofloxacin 500 to 750 mg twice daily should be considered if there is a history of infection with *Pseudomonas aeruginosa*. Patients who have cultured methicillin-resistant *Staphylococcus aureus* may be treated with a combination of rifampicin and fucidin, tetracycline-based antibiotics, or linezolid.

Intravenous Antibiotic Treatment for Pulmonary Exacerbations

Intravenous antibiotics are indicated for patients with severe exacerbations or exacerbations that fail to resolve with oral antibiotic treatment. This usually involves admission to hospital, but many centers offer community-based intravenous antibiotic programs that allow patients to have all or a proportion of their treatment at home or in infusion centers. This is particularly relevant for patients with educational, work, or family commitments. It can also be a more cost-effective option for the health care provider. If self-administering treatment at home, patients must demonstrate that they are competent at intravenous drug administration and should have an appropriate domestic environment. Most centers recommend that the first dose is administered in hospital to ensure patients can infuse the antibiotic correctly and to ensure that there are no adverse reactions. Robust systems need to be in place to monitor drug levels in patients prescribed aminoglycosides and careful monitoring of renal function is essential in patients receiving potentially nephrotoxic drugs.

Intravenous access for antibiotic administration during bronchiectasis exacerbations can be achieved through use of peripheral cannulas, long lines, peripherally inserted central catheters (PICC), and totally implantable venous access devices (TIVAD). PICCs and TIVADs are particularly useful in patients with difficult peripheral access who require frequent courses of intravenous treatment; however, these devices require regular flushing and need to be looked after carefully. Potential complications include thrombosis and infection, particularly in higher risk groups such

Table 1
Common organisms associated with acute exacerbation of bronchiectasis and suggested antimicrobial agents in adults

Organism	Recommended First-Line Treatment	Length of Treatment	Recommended Second-Line Treatment	Length of Treatment
Streptococcus pneumoniae	Amoxicillin 500 mg 3 times a day	14 d	Doxycycline 100 mg BD	14 d
Haemophilus influenzae- beta lactamase negative	Amoxicillin 500 mg 3 times a day Or amoxicillin 1 g 3 times a day Or amoxicillin 3 g BD	14 d	Doxycycline 100 mg BD Or ciprofloxacin 500 mg or 750 mg BD or ceftriaxone 2 g OD (IV)	14 d
H influenzae- beta lactamase positive	Amoxicillin with clavulanic acid 625 mg TDS	14 d	Doxycycline 100 mg BD or ciprofloxacin 500 mg or 750 mg BD or ceftriaxone 2 g OD (IV)	14 d
Moraxella catarrhalis	Amoxicillin with clavulanic acid 625 mg TDS	14 d	Clarithromycin 500 mg BD or doxycycline 100 mg BD or ciprofloxacin 500 mg or 750 mg BD	14 d
Staphylococcus aureus (MSSA)	Flucloxacillin 500 mg QDS	14 d	Clarithromycin 500 mg BD or doxycycline 100 mg BD or amoxicillin with clavulanic acid 625 mg TDS	14 d
S aureus (MRSA) Oral preparations	Doxycycline 100 mg BD or Rifampicin (<50 kg) 450 mg OD or Rifampicin (>50 kg) 600 mg OD or Trimethoprim 200 mg BD	14 d	Third-line linezolid 600 mg BD	14 d
S aureus (MRSA) Intravenous preparations	Vancomycin 1 g BD[a] (monitor serum levels and adjust dose accordingly) or teicoplanin 400 mg OD	14 d	Linezolid 600 mg BD	14 d
Coliforms for example, *Klebsiella*, *Enterobacter*	Oral ciprofloxacin 500 mg or 750 mg BD	14 d	Intravenous ceftriaxone 2 g OD	14 d

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Table 1
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Organism	Recommended First-Line Treatment	Length of Treatment	Recommended Second-Line Treatment	Length of Treatment
Pseudomonas aeruginosa	Oral ciprofloxacin 500 mg BD (750 mg BD in more severe infections)	14 d	**Monotherapy:** Intravenous ceftazidime 2 g TDS or piperacillin with tazobactam 4.5 g TDS or aztreonam 2 g TDS or meropenem 2 g TDS	14 d
			Combination therapy: The above can be combined with gentamicin or tobramycin or colistin 2MU TDS (under 60 kg, 50,000–75,000 Units/kg daily in 3 divided doses)	
			Patients can have an in vivo response despite in vitro resistance. Caution with aminoglycosides as highlighted below but also if previous adverse events, particularly previous ototoxicity/ acute kidney injury due to aminoglycosides	

Caution with aminoglycosides in pregnancy, renal failure, elderly, or on multiple other drugs.

Abbreviations: BNF 72 (March 2017); BD, twice daily; IV, intravenous; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *S aureus*; OD, once daily; BD, twice daily; TDS, three times daily; QDS, four times daily.

[a] Elderly (older than 65 y), 500 mg vancomycin every 12 h or 1 g OD.

From Hill AT, Sullivan AL, Chalmers JD, De Soyza A, Elborn SJ, Floto AR, Grillo L, Gruffydd-Jones K, Harvey A, Haworth CS, Hiscocks E, Hurst JR, Johnson C, Kelleher PW, Bedi P, Payne K, Saleh H, Screaton NJ, Smith M, Tunney M, Whitters D, Wilson R, Loebinger MR. British Thoracic Society Guideline for bronchiectasis in adults. Thorax. 2019 Jan;74(Suppl 1):1-69.

as the elderly and those with primary or secondary immunodeficiency syndromes.

Intravenous antibiotic choices should be based on historic sputum culture results; potential regimens are outlined in **Table 1**.[15] Empiric antibiotic treatment may include ceftriaxone, unless patients are thought likely to be infected with *P aeruginosa*. However, as the efficacy of beta-lactam antibiotics is related to the time above the minimum inhibitory concentration, once-daily antibiotics may be less effective than thrice-daily antibiotics, as a satisfactory intraluminal antibiotic concentration needs to be maintained in the context of sputum-filled airways and biofilm formation.

Intravenous Antibiotic Treatment for Pseudomonas aeruginosa Infection

Empiric antibiotic treatment in patients with *P aeruginosa* infection may include a beta-lactam, such as ceftazidime.[15] Monotherapy may suffice in patients infected with a fully sensitive organism, but in the context of a resistant organism or chronic infection in which patients may require multiple treatment courses in the future, dual therapy with an aminoglycoside may reduce the risk of antibiotic resistance, as well as provide synergistic benefits.[16,17] In a study evaluating the effect of intravenous azlocillin + placebo versus intravenous azlocillin + tobramycin in patients with cystic fibrosis, initial clinical outcomes were comparable, but there was a greater reduction in *P aeruginosa* sputum density, and time to next hospitalization was significantly increased in the group receiving dual therapy.[18] These data suggest that dual antibiotic therapy is preferable in patients with chronic *P aeruginosa* infection, as long as they do not have relevant comorbidities. The risk of renal impairment, ototoxicity, and vestibular damage appears to be greater with gentamicin than tobramycin.[19,20] Although once-daily versus thrice-daily tobramycin dosing in children with cystic fibrosis appears to offer equivalent clinical outcomes and reduced renal toxicity,[21] the most appropriate dosing regimen has not been established in adults with bronchiectasis.

The role of antibiotic susceptibility testing in patients with bronchiectasis and chronic *P aeruginosa* infection is contentious because of the poor correlation between in vitro antibiotic sensitivity test results and clinical outcomes.[22,23] Foweraker and colleagues[22] studied sputum samples from patients with cystic fibrosis and found an average of 4 *P aeruginosa* morphotypes per sputum sample and 3 distinct antibiotic susceptibility profiles per morphotype. Forty-eight colonies with varying antibiotic susceptibility profiles were cultured from 1 sputum sample, and it was noted that susceptibility profiles of single *P aeruginosa* isolates correlated poorly with pooled cultures, with the pooled cultures underestimating levels of antibiotic resistance. Foweraker and colleagues[22] also showed that susceptibility results from 1 sputum sample tested in duplicate by 8 biomedical scientists within 1 laboratory and by biomedical scientists in 7 other laboratories did not correlate well. These data are supported by the findings of Smith and colleagues,[24] who showed no correlation between the susceptibility of *P aeruginosa* to ceftazidime or tobramycin and clinical response to these antibiotics in 77 chronically infected patients with cystic fibrosis. Furthermore, a randomized controlled trial evaluating clinical outcomes using multiple combination bactericidal testing versus clinician preference to guide intravenous antibiotic choices to manage cystic fibrosis pulmonary exacerbations showed no advantage in using the more sophisticated microbiological tests.[25] Based on the preceding evidence, a pragmatic approach is required when choosing antibiotic combinations for patients with bronchiectasis and chronic *P aeruginosa* infection. Common practice is to choose 2 antipseudomonal antibiotics (usually a beta-lactam in combination with tobramycin) to which most morphotypes are sensitive. An alternative approach involves basing antibiotic choices predominantly on what has worked well for the patient in the past.

The potential for drug-drug interactions, general toxicity (liver, renal, bone marrow, audiological, QT interval), and gastrointestinal complications (including *Clostridium difficile* colitis) needs to be considered on a case-by-case basis when choosing the most appropriate oral or intravenous antibiotic regimen.

MAINTENANCE ANTIBIOTIC TREATMENT IN ADULTS WITH BRONCHIECTASIS

Maintenance antibiotics are prescribed in patients with bronchiectasis to improve symptoms, reduce exacerbation frequency, and optimize quality of life through reducing bacterial load and airway inflammation. Macrolide antibiotics also may have immunomodulatory effects through reducing neutrophil-mediated lung damage.[26]

Antibiotics used on a long-term basis are usually administered orally or through inhalation, although in patients with severe bronchiectasis, elective courses of intravenous treatment may offer benefit. In a single-center study involving 19 patients with a history of 5 or more exacerbations per year, 8 weekly courses of intravenous antibiotics for 12 months were associated with a small but

statistically significant improvement in exacerbation frequency compared with the previous year.[27]

Oral Maintenance Antibiotic Treatment in Adults with Bronchiectasis

Oral maintenance antibiotic treatment in patients with bronchiectasis was first evaluated in the 1950s, the most notable study being performed by the Medical Research Council in which 122 subjects were randomized to receive penicillin, oxytetracycline, or placebo.[28] The antibiotics were formulated as identical 0.25-g capsules, and patients were prescribed 2 capsules 4 times a day on 2 days each week for 1 year. Oxytetracycline treatment was associated with a decrease in sputum volume to 64% of pretreatment levels, and the purulent fraction decreased by 50%. Use of oxytetracycline was also associated with fewer days off work and days confined to bed. The outcomes reported in patients allocated to the penicillin and placebo groups suggested that oxytetracycline was the more effective intervention, although formal statistical analysis was not performed, and sputum microbiology data were not reported. Subsequent studies in the 1950s and 1960s provided further support for the use of long-term tetracycline/penicillin-based antibiotic regimens in patients with bronchiectasis.[29,30] However, the latter study noted an increase in the culture of *Pseudomonas* and *Proteus* species, suggesting that the lung microbiome may be altered by maintenance antibiotic treatment.

The impact of high-dose amoxicillin was evaluated in 38 patients with bronchiectasis randomized to receive amoxicillin 3 g or placebo twice daily for 32 weeks.[31] Diary card data showed that a higher proportion of patients improved in the amoxicillin group (11 of 17) compared with the placebo group (4 of 19), and patients in the amoxicillin group also spent significantly less time confined to bed and away from work compared with the placebo group. Although the exacerbation frequency was similar in the treatment and placebo groups, the episodes were less severe in the amoxicillin group compared with before the study was started. The decrease in purulent sputum volume was greater in the amoxicillin group (20% of pretreatment volume) compared with the placebo group (88% of pretreatment volume). Adverse events leading to discontinuation of study drug included rash in 1 patient in the amoxicillin group and diarrhea in 1 patient from each group. There was a trend toward greater antibiotic resistance in patients treated with amoxicillin. No patients developed *C difficile*–related diarrhea.

In a 4-month open-label study of oral and nebulized amoxicillin involving 10 patients with bronchiectasis and variable sputum microbiology (predominantly *Haemophilus influenzae*), antibiotic treatment was associated with a reduction in sputum purulence and volume, a reduction in sputum inflammatory indices, increases in lung function, and improved patient-reported outcomes.[32] After treatment cessation, sputum purulence reemerged after a median of 2.5 months.

Rayner and colleagues[33] reported the microbiological outcomes of 10 patients with bronchiectasis who had been prescribed more than 90 days of continuous oral ciprofloxacin. Following treatment, 6 patients (who previously had sputum cultures of *P aeruginosa* [n = 2], *H influenzae* [n = 3], or no organism [n = 1]) had sterile sputum cultures. In the remaining 4 subjects, *P aeruginosa* was replaced by *Streptococcus pneumoniae* in 1 person, 2 people continued to culture *P aeruginosa* (which had become resistant to ciprofloxacin), and *S pneumoniae* persisted in 1 person. Although exacerbation frequency and hospital admissions decreased on treatment, the development of ciprofloxacin-resistant strains of *P aeruginosa* is a concern, particularly as this coincided with an exacerbation that required inpatient treatment with intravenous antibiotics.

More recently, 3 randomized placebo-controlled studies evaluated the impact of macrolide antibiotics in patients with bronchiectasis.[34–36] In the trial by Wong and colleagues,[34] 141 patients with bronchiectasis and a history of at least 1 exacerbation requiring antibiotic treatment in the preceding 12 months were randomized to azithromycin 500 mg or placebo 3 times per week for 6 months. The rate of event-based exacerbations was 0.59 per patient in the azithromycin group and 1.57 per patient in the placebo group in the 6-month treatment period (rate ratio 0.38, 95% confidence interval [CI] 0.26–0.54; $P<.0001$), and the impact on exacerbation frequency remained 6 months after stopping study drug. There were no significant changes in quality of life as measured by the St George's Respiratory Questionnaire (SGRQ) total score, but there was a significant improvement after 6-month treatment in the symptom component of the SGRQ in patients receiving azithromycin. In the trial by Altenburg and colleagues,[35] 83 patients with a history of bronchiectasis and 3 or more exacerbations in the preceding year were randomized to azithromycin 250 mg or placebo daily for 12 months. At the end of the study, the median (interquartile range) number of exacerbations in the azithromycin group was 0 (0–1) compared with 2 (1–3) in the placebo group ($P<.001$). Gastrointestinal adverse

effects occurred in 40% of patients in the azithromycin group and in 5% in the placebo group (relative risk, 7.44 [95% CI, 0.97–56.88] for abdominal pain and 8.36 [95% CI, 1.10–63.15] for diarrhea), but without need for discontinuation of study treatment. Macrolide resistance was noted in 88% of azithromycin-treated individuals compared with 26% in the placebo group. In the trial by Serisier and colleagues,[36] 117 patients with bronchiectasis and 2 or more exacerbations in the preceding year were randomized to erythromycin 400 mg or placebo twice daily for 12 months. At the end of the study, the mean number of pulmonary exacerbations per patient per year was 1.29 (95% CI, 0.93–1.65) in the erythromycin group compared with 1.97 (95% CI, 1.45–2.48) in the placebo group (incidence rate ratio, 0.57; 95% CI, 0.42–0.77; $P = .003$). Erythromycin treatment was also associated with a significant increase in macrolide-resistant oropharyngeal streptococci.

An individual participant data meta-analysis of these 3 randomized controlled trials of macrolide antibiotics in adults with bronchiectasis confirmed that macrolide antibiotics reduce exacerbation frequency, with an adjusted incidence rate ratio 0.49 (95% CI, 0.36–0.66, $P<.0001$).[37] Although the improvement in quality of life measured by the SGRQ did not exceed the minimum clinically important difference, the proportion of patients who achieved a clinically meaningful improvement in quality of life was increased in the macrolide group compared with the placebo group. The study also showed that macrolides are effective in patients with a low exacerbation frequency (1 or more in the year preceding treatment) and in patients with *P aeruginosa*.

Nebulized Maintenance Antibiotic Treatment in Adults with Bronchiectasis

The inhaled route of antibiotic administration offers the potential to deliver high concentrations of antibiotic directly to the site of infection. Although antibiotic-induced airway irritation can result in bronchoconstriction/intolerance in some individuals, the risk of systemic toxicity is greatly reduced compared with oral and intravenous antibiotic administration, which is an important factor in the context of the comorbidities often seen in patients with bronchiectasis.[38] To date, international phase III randomized placebo-controlled studies evaluating nebulized aztreonam lysine (AZLI),[39] dry powder ciprofloxacin,[40,41] and nebulized liposomal ciprofloxacin[42] in patients with bronchiectasis have been reported.

Nebulized AZLI was evaluated in 2 double-blind, multicenter, randomized placebo-controlled phase 3 trials (AIR-BX −1 and −2), which included patients aged 18 years or older who had bronchiectasis and history of positive sputum or bronchoscopic culture for target gram-negative organisms (species of *Pseudomonas*, *Achromobacter*, *Burkholderia*, *Citrobacter*, *Enterobacter*, *Escherichia*, *Klebsiella*, *Moraxella*, *Proteus*, *Serratia*, and *Stenotrophomonas*).[39] Patients were randomly assigned to receive either AZLI or placebo (1:1) and received two 4-week courses of AZLI 75 mg or placebo 3 times daily through the eFlow nebulizer, each followed by a 4-week off-treatment period. The primary endpoint was change from baseline Quality of Life-Bronchiectasis Respiratory Symptoms scores (QOL-B-RSS) after the first 4 weeks of treatment. A total of 540 patients were randomized. The difference between AZLI and placebo for adjusted mean change from baseline QOL-B-RSS was not significant at 4 weeks (0.8 [95% CI –3.1 to 4.7], p=0.68) in AIRBX1, but was significant (4.6 [1.1 to 8.2], p=0.011) in AIR-BX2. However, the 4.6-point difference in QOL-B-RSS after 4 weeks in AIR-BX2 was not deemed clinically significant. In both studies, treatment-related adverse events were more common in the AZLI group than in the placebo group, as were discontinuations from adverse events.

Ciprofloxacin Dry Powder for Inhalation (DPI) was evaluated in 2 double-blind, multicenter, randomized placebo-controlled phase 3 trials (Respire-1 and -2), which included patients with bronchiectasis, 2 or more exacerbations in the preceding 12 months, and a positive sputum culture at screening for at least 1 of the following organisms: *P aeruginosa*, *H influenzae*, *Moraxella catarrhalis*, *S aureus*, *S pneumoniae*, *Stenotrophomonas maltophilia,* or *Burkholderia cepacia*).[40,41] A total of 937 patients were randomized 2:1 to twice-daily ciprofloxacin DPI 32.5 mg or placebo in 2 treatment regimens consisting of on/off treatment cycles of 14 or 28 days for 48 weeks. The primary endpoints were time to first exacerbation and frequency of exacerbations. In Respire-1, ciprofloxacin DPI 14 days on/off significantly prolonged time to first exacerbation versus pooled placebo (median time >336 vs 186 days; hazard ratio 0.53, 97.5% CI 0.36–0.80; $P = .0005$) and reduced the frequency of exacerbations compared with matching placebo by 39% (mean number of exacerbations 0.6 vs 1.0; incidence rate ratio 0.61, 97.5% CI 0.40–0.91; $P = .0061$). Outcomes for ciprofloxacin DPI 28 days on/off were not statistically significantly different from placebo. In Respire-2, the exacerbation rate was low across treatment arms (mean ± SD 0.6 ± 0.9) and there were no statistically significant differences

between active treatment and placebo. Ciprofloxacin DPI was well tolerated in both studies.

Nebulized liposomal ciprofloxacin (ARD-3150) was evaluated in 2 double-blind, multicenter, randomized placebo-controlled phase 3 trials (ORBIT-3 and -4), which included patients with bronchiectasis with 2 or more exacerbations treated with antibiotics in the preceding 12 months and a history of chronic *P aeruginosa* infection.[42] A total of 582 patients were randomly assigned (2:1) to receive either ARD-3150 or placebo. ARD-3150 (3 mL liposome encapsulated ciprofloxacin 135 mg and 3 mL free ciprofloxacin 54 mg) or placebo (3 mL dilute empty liposomes mixed with 3 mL of saline) was self-administered once daily for 6 treatment cycles (28 days on and 28 days off treatment) over 48 weeks. The primary endpoint was time to first pulmonary exacerbation. In ORBIT-4, the median time to first pulmonary exacerbation was 230 days in the ARD-3150 group compared with 158 days in the placebo group (hazard ratio [HR] 0.72; 95% CI, 0.53–0.97], $P = 0.032$). In ORBIT-3, the median time to first pulmonary exacerbation was 214 days in the ARD-3150 group and 136 days in the placebo group (HR 0.99; 95% CI, 0.71–1.38; $P = 0{\cdot}97$). ARD-3150 was well tolerated in both studies.

A systematic review and meta-analysis of inhaled antibiotic treatment in adults with bronchiectasis analyzed 16 trials involving data from 2597 patients.[43] The mean reduction of colony-forming units with inhaled antibiotics was −2.32 log units (95% CI, –3.20 to −1.45; $P<.0001$) per g/sputum. Bacterial eradication was increased with inhaled antibiotic therapy (odds ratio [OR] 3.36; 1.63–6.91; $P = .0010$). Inhaled antibiotics significantly reduced exacerbation frequency (rate ratio 0.81; 0.67–0.97; $P = .020$). Time to first exacerbation was significantly prolonged with inhaled antibiotics (HR 0.83; 0.69–0.99; $P = .028$). The proportion of patients with at least 1 exacerbation decreased (risk ratio 0.85; 0.74–0.97; $P = .015$). There was a significant reduction in the frequency of severe exacerbations (rate ratio 0.43; 0.24–0.78; $P = .0050$). The scores for neither the Quality-of-Life Bronchiectasis questionnaire nor the SGRQ improved above the minimal clinically important difference. The relative change in forced expiratory volume in 1 second was a deterioration of 0.87% (–2.00 to 0.26%; p=0.13). There was no difference in treatment-emergent adverse effects (OR 0.97; 0.67–1.40; $P = .85$) or bronchospasm (0.99; 0.66–1.48; $P = .95$). Emergence of bacterial resistance was evident at the end of the treatment period (risk ratio 1.91; 1.46–2.49; $P<.0001$). Thus, based on current data, use of inhaled antibiotics appears to result in a modest reduction in total exacerbation frequency, and a more clinically meaningful reduction in the frequency of severe exacerbations.

There are a number of potential explanations for the inconsistent outcomes reported in these large phase III inhaled antibiotic programs. First and foremost, bronchiectasis is a heterogeneous condition, and it is clear that some patients are more likely to benefit from inhaled antibiotics than others. For example, a post hoc analysis of the AIR-BX studies revealed that patients with a high baseline bacterial load ($\geq 10^7$ colony-forming units/g sputum) had a statistically and clinically meaningful improvement in respiratory symptoms after 4-week and 12-week treatment in contrast to those patients with lower bacterial loads,[44] suggesting that future studies of inhaled antibiotics should prioritize enrollment of patients with high bacterial loads to enrich the study population with those most likely to respond. Second, the regimen used (cyclical vs continuous) appears to be an influential factor. As a high bacterial load is associated with increased airway inflammation, an increased risk of exacerbation and a worse quality of life,[11,44] it is perhaps not surprising that trials using a cyclical treatment regimen have shown more inconsistent results than studies using a continuous treatment regimen.[45,46] This concept is further supported by data from the phase II study of Tobramycin Inhalation Powder (TIP) in patients with bronchiectasis in whom the area under the curve reduction in *P aeruginosa* bacterial load was significantly greater in patients receiving continuous versus cyclical TIP[47] and by a post hoc analysis of the ORBIT studies, which showed that treatment with liposomal ciprofloxacin resulted in a significant improvement in respiratory symptoms during on-treatment periods and that changes in respiratory symptoms were correlated with changes in bacterial load.[48] Third, the primary outcome measure in the ORBIT studies and the co-primary endpoint in the RESPIRE studies was time to first exacerbation. This endpoint could be influenced by an imbalance in the baseline exacerbation frequency in the treatment and placebo groups, as frequent exacerbations are the best predictor of future exacerbations.[49] An imbalance between groups in the time to previous exacerbation could also interfere with the time to first exacerbation endpoint. However, recognizing that annualized exacerbation rate is likely to better reflect the impact of treatment during a 12-month trial, regulators in the United States and Europe now appear to favor annualized exacerbation rate over time to first exacerbation as the primary outcome measure. Fourth, the duration of treatment is likely to

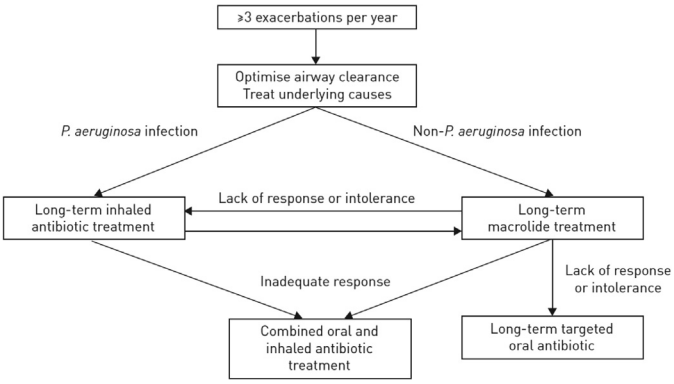

Fig. 1. Summary of recommendations for long-term antibiotic treatment in adults with bronchiectasis.[14] (*From* Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017 Sep 9;50(3):1700629.)

impact on outcomes. For example, the benefits of nebulized colistin on quality of life only became apparent after 3 months of continuous treatment,[45] whereas the AZLI study evaluated outcomes after only 28 days of treatment.[39] Fifth, the exacerbation frequency in the placebo groups of many of the phase III studies has been much less than the reported exacerbation frequency before the trial, suggesting that recall of prior exacerbation frequency is inaccurate, or that the threshold for protocol-defined exacerbations in trials is harder to achieve than in routine clinical practice, or that patients do not wish to declare exacerbations, perhaps because they do not want to visit their study center when they are unwell. Enabling phone reporting of exacerbations or retrospective reporting of exacerbations may increase the reporting of events. Sixth, cultural/geographic factors may influence the frequency of exacerbations recorded in clinical trials, as tolerance of symptoms is likely to vary region to region, as is the prevalence of other factors such as coexisting chronic obstructive pulmonary disease, which is associated with a higher exacerbation frequency.

Maintenance Antibiotics in Clinical Practice

The European Respiratory Society bronchiectasis guidelines suggest offering long-term antibiotic treatment to patients with 3 or more exacerbations per year.[14] This threshold is loosely based on the baseline exacerbation frequency of participants in the 3 main macrolide treatment trials.[34–36] The prescription of long-term oral antibiotics also may be considered in patients with (1) infrequent but very severe exacerbations, (2) comorbidities such as primary or secondary immunodeficiency or are immunosuppressed for other reasons, (3) exacerbations that have a significant impact on their quality of life, or (4) in patients with severe bronchiectasis.[14]

Before considering long-term antibiotics, it is important to ensure that all other areas of bronchiectasis care have been optimized, such as airway clearance and addressing underlying conditions that may predispose patients to having exacerbations, such as active allergic bronchopulmonary aspergillosis, an untreated immunodeficiency syndrome or unrecognized nontuberculous mycobacterial-lung disease (NTM-LD). The latter is particularly important to identify before the prescription of macrolides or inhaled aminoglycosides to prevent the development of drug resistance through the inadvertent prescription of monotherapy for NTM-LD. It is also essential to determine the sputum microbiology before and after implementation of long-term antibiotics to direct antibiotic choices, monitor for the development of resistance, and to identify treatment-emergent organisms. Screening for comorbidities before the prescription of long-term antibiotics is also important, particularly with azithromycin in relation to preexisting tinnitus, hearing impairment, vestibular problems, and QT prolongation, which may contraindicate treatment.

A suggested algorithm for use of long-term antibiotics has been published in the European bronchiectasis guidelines (shown in **Fig. 1**).[14] Broadly speaking, inhaled antibiotics such as colistin or gentamicin should be considered for patients with chronic *P aeruginosa* infection, and macrolides should be considered in non-*Pseudomonas* patients or in *Pseudomonas*-infected patients in whom inhaled antibiotics are ineffective, contraindicated, not tolerated, or not feasible.[14] However, a recent meta-analysis of individual participant data from the 3 main macrolide studies in bronchiectasis has challenged this approach by showing that there is a high level of benefit of using macrolides in patients with *P aeruginosa* infection.

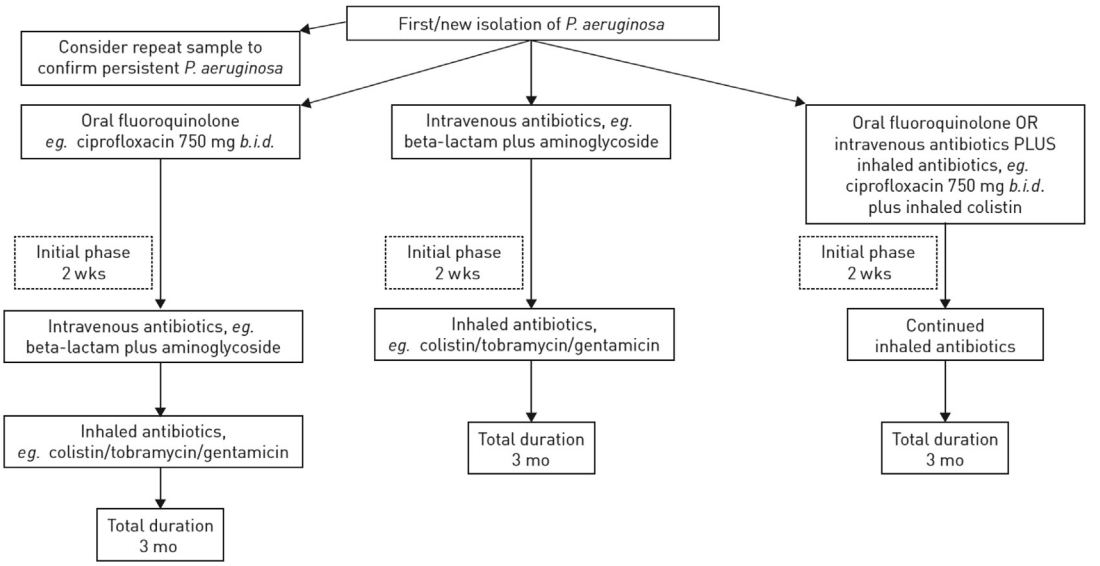

Fig. 2. Three possible and alternative eradication treatment pathways based on what is commonly used in clinical practice in adults with bronchiectasis. After each step, it is recommended to repeat sputum sampling for *P aeruginosa* and to progress to the next step if the culture remains positive.[14] (*From* Polverino E, Goeminne PC, McDonnell MJ, Aliberti S, Marshall SE, Loebinger MR, Murris M, Cantón R, Torres A, Dimakou K, De Soyza A, Hill AT, Haworth CS, Vendrell M, Ringshausen FC, Subotic D, Wilson R, Vilaró J, Stallberg B, Welte T, Rohde G, Blasi F, Elborn S, Almagro M, Timothy A, Ruddy T, Tonia T, Rigau D, Chalmers JD. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J. 2017 Sep 9;50(3):1700629.)

Although only 61 (18%) of 341 participants had *P aeruginosa*, the estimated effect in these patients was a significant reduction in exacerbation frequency (0.36; CI, 0.18–0.72; $P = .0044$), perhaps suggesting that based on the current evidence, macrolides should be used first line in place of inhaled antibiotics in patients with *P aeruginosa* infection.

ERADICATING NEW GROWTHS OF SPECIFIC ORGANISMS IN ADULTS WITH BRONCHIECTASIS

In clinical practice, eradication regimens are often prescribed following identification of new growths of *P aeruginosa* because of the increased morbidity and mortality associated with chronic infection.[50] There is only 1 randomized trial to date evaluating an eradication regimen. In this study, 35 patients with bronchiectasis and a first growth of *P aeruginosa* were randomized to receive 2 weeks of ceftazidime and tobramycin followed by either nebulized tobramycin 300 mg or placebo twice daily for 3 months.[51] The proportion free of *P aeruginosa* after 12 months of follow-up in the nebulized tobramycin and placebo groups was 55% and 29%, respectively. There were also significant reductions in exacerbation frequency and hospitalization in the nebulized tobramycin group. Five patients in the nebulized tobramycin group discontinued treatment because of bronchospasm and 2 patients in the placebo group withdrew from the study. The emergence of tobramycin-resistant isolates was not observed.

Some of the oral and nebulized antibiotic studies in patients with bronchiectasis report variable success rates in eradicating *P aeruginosa*, but these studies were not designed to address this specific issue and largely involved patients with chronic *P aeruginosa* infection.

The European Respiratory Society guidelines recommend that adults with bronchiectasis and a new growth of *P aeruginosa* should be offered eradication treatment, but not following new growth of other organisms.[14] This is in contrast to the British Thoracic Society guidelines that also recommend eradication treatment following a new growth of methicillin-resistant *S aureus*.[15] The European Respiratory Society guideline offers 3 different antibiotic regimens to treat new isolations of *P aeruginosa,* and these are shown in Fig. 2.[14]

SUMMARY

Antibiotics play a crucial role in the management of patients with bronchiectasis through reducing sputum bacterial load, minimizing endobronchial

inflammation, and therefore probably preventing airway wall damage. Antibiotics can be used for treatment of exacerbations, for maintenance therapy to reduce exacerbation frequency, and for eradicating potentially harmful organisms such as *P aeruginosa*. Antibiotic choices should be based on sputum microbiological results. Careful monitoring is required to track microbial resistance patterns, detect the emergence of new bacteria and fungi, and to quickly identify gastrointestinal complications and antibiotic-related toxicity (particularly with macrolides and aminoglycosides). In the future, the options for maintenance antibiotic therapy are likely to increase through the development of new nebulized and dry powder formulations.

CLINICS CARE POINTS

- Azithromycin reduces exacerbation frequency in patients with bronchiectasis.
- Rule out co-existing non-tuberculous mycobacterial infection before initiating maintenace azithromycin treatment.
- Monitor the QT interval and warn patients about the potential for tinnitus, hearing loss and vestibular problems with maintenance azithromycin treatment.

DISCLOSURE

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REFERENCES

1. Reid LM. Reduction in bronchial subdivision in bronchiectasis. Thorax 1950;5:233–47.
2. Cole PJ. Inflammation: a two-edge sword – the model of bronchiectasis. Eur J Respir Dis 1986;69:6–15.
3. Flume PA, Chalmers JD, Olivier KN. Advances in bronchiectasis: endotyping, genetics, microbiome and disease heterogeneity. Lancet 2018;392(10150):880–90. https://doi.org/10.1016/S0140-6736(18)31767-7.
4. Hill AT, Haworth CS, Aliberti S, et al. Pulmonary exacerbation in adults with bronchiectasis: a consensus definition for clinical research. Eur Respir J 2017;49(6):1700051. https://doi.org/10.1183/13993003.00051-2017.
5. Hill SL, Morrison HM, Burnett D, et al. Short term response of patients with bronchiectasis to treatment with amoxicillin given in standard or high doses orally or by inhalation. Thorax 1986;41:559–65.
6. Ip M, Shum D, Lauder I, et al. Effect of antibiotics on sputum inflammatory contents in acute exacerbations of bronchiectasis. Respir Med 1993;87:449–54.
7. Tsang KWT, Chan W-M, Ho P-L, et al. A comparative study on the efficacy of levofloxacin and ceftazidime in acute exacerbation of bronchiectasis. Eur Resp J 1999;14:1206–9.
8. 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;130:1503–10.
9. Courtney JM, Kelly MG, Watt A, et al. Quality of life and inflammation in exacerbations of bronchiectasis. Chron Respir Dis 2008;5(3):161–8.
10. Murray MP, Turnball K, MacQuarrie, et al. Assessing response to treatment of exacerbations of bronchiectasis in adults. *Eur Respir* J 2009;33:312–7.
11. 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. https://doi.org/10.1164/rccm.201203-0487OC.
12. Stockley RA, Hill SL, Morrison HM. Effect of antibiotic treatment on sputum elastase in bronchiectatic outpatients in a stable clinical state. Thorax 1984;39:414–9.
13. Hill SL, Stockley RA. Effect of short and long term antibiotic response on lung function in bronchiectasis. Thorax 1986;41:798–800.
14. Polverino E, Goeminne PC, McDonnell MJ, et al. European Respiratory Society guidelines for the management of adult bronchiectasis. Eur Respir J 2017;50(3):1700629. https://doi.org/10.1183/13993003.00629-2017.
15. Hill AT, Sullivan AL, Chalmers JD, et al. British Thoracic Society guideline for bronchiectasis in adults. Thorax 2019;74(Suppl 1):1–69.
16. Cheng K, Smyth RL, Govan JR, et al. Spread of a beta-lactam-resistant *Pseudomonas aeruginosa* in a cystic fibrosis clinic. Lancet 1996;348:639–42.
17. Elphick HE, Tan A. Single versus combination intravenous antibiotic therapy for people with cystic fibrosis. Cochrane Database Syst Rev 2005;18(2):CD002007.
18. Smith AL, Doershuk C, Goldman D, et al. Comparison of a beta-lactam alone versus beta-lactam and an aminoglycoside for pulmonary exacerbation in cystic fibrosis. J Pediatr 1999;134:413–21.
19. Bertenshaw C, Watson AR, Lewis S, et al. Survey of acute renal failure in patients with cystic fibrosis in the UK. Thorax 2007;62:541–5.

20. Smyth A, Lewis S, Bertenshaw C, et al. Case-control study of acute renal failure in patients with cystic fibrosis in the UK. Thorax 2008;63:532–5.
21. Smyth A, Tan KH, Hyman-Taylor P, et al, TOPIC Study Group. Once versus three-times daily regimen of tobramycin for pulmonary exacerbations of cystic fibrosis – the TOPIC study: a randomised controlled trial. Lancet 2005;365:573–8.
22. Foweraker JE, Laughton CR, Brown DFJ, et al. Phenotypic variability of *Pseudomonas aeruginosa* in sputa from patients with acute infective exacerbation of cystic fibrosis and its impact on the validity of antimicrobial susceptibility testing. J Antimicrob Chemother 2005;55:921–7.
23. Gillham MI, Sundaram S, Laughton CR, et al. Variable antibiotic susceptibility in populations of *Pseudomonas aeruginosa* infecting patients with bronchiectasis. J Antimicrob Chemother 2009;63:728–32.
24. Smith AL, Fiel S, Mayer-Hamblett N, et al. Susceptibility testing of *Pseudomonas aeruginosa* isolates and clinical response to parenteral antibiotic administration. Lack of association in cystic fibrosis. Chest 2003;123:1495–502.
25. Aaron SD, Vandemheen KL, Ferris W, et al. Combination antibiotic sensitivity testing to treat exacerbations of cystic fibrosis associated with multiresistant bacteria: a randomised, double-blind, controlled clinical trial. Lancet 2005;366:463–71.
26. Haworth CS, Bilton D, Elborn JS. Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. Respir Med 2014;108:1397–408.
27. Mandal P, Sidhu MK, Donaldson LS, et al. Eight-weekly intravenous antibiotics is beneficial in severe bronchiectasis. QJM 2013;106(1):27–33.
28. Medical Research Council. Prolonged antibiotic treatment of severe bronchiectasis; a report by a subcommittee of the antibiotics clinical trials (non-tuberculous) committee of the Medical Research Council. BMJ 1957;2:255–9.
29. Cherniack NS, Vosti KL, Dowling HF, et al. Long-term treatment of bronchiectasis and chronic bronchitis. A.M.A. Arch Intern Med 1959;103:345–53.
30. Dowling HF, Mellody M, Lepper MH, et al. Bacteriologic studies of the sputum in patients with chronic bronchitis and bronchiectasis. Results of continuous therapy with tetracycline, penicillin, or an oleandromycin-penicillin mixture. Am Rev Respir Dis 1960;81:329–39.
31. Currie DC, Garbett ND, Chan KL, et al. Double-blind randomized study of prolonged higher-dose oral amoxicillin in purulent bronchiectasis. Q J Med 1990;76:799–816.
32. Hill SL, Burnett D, Hewetson KA, et al. The response of patients with purulent bronchiectasis to antibiotics for four months. Q J Med 1988;250:163–73.
33. Rayner CFJ, Tillotson G, Cole PJ, et al. Efficacy and safety of long-term ciprofloxacin in the management of severe bronchiectasis. J Antimicrob Chemother 1994;34:149–56.
34. 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;380:660–7.
35. 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;309:1251–9.
36. 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. JAMA 2013;309:1260–7.
37. Chalmers JD, Boersma W, Lonergan M, et al. Long-term macrolide antibiotics for the treatment of bronchiectasis in adults: an individual participant data meta-analysis. Lancet Respir Med 2019;7:845–54.
38. McDonnell MJ, Alberti S, Goeminne PC, et al. Comorbidities and the risk of mortality in patients with bronchiectasis: an international cohort study. Lancet Respir Med 2016;4(12):969–79. https://doi.org/10.1016/S2213-2600(16)30320-4.
39. 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;2:738–49.
40. De Soyza A, Aksamit T, Bandel TJ, et al. Respire 1: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J 2018;51:1702052.
41. Aksamit T, De Soyza A, Bandel TJ, et al. Respire 2: a phase III placebo-controlled randomised trial of ciprofloxacin dry powder for inhalation in non-cystic fibrosis bronchiectasis. Eur Respir J 2018;51:1702053.
42. Haworth CS, Bilton D, Chalmers JD, et al. Inhaled liposomal ciprofloxacin in patients with non-cystic fibrosis bronchiectasis and chronic lung infection with Pseudomonas aeruginosa (ORBIT-3 and ORBIT-4): two phase 3, randomised controlled trials. Lancet Respir Med 2019;7(3):213–26. https://doi.org/10.1016/S2213-2600(18)30427-2.
43. Laska IF, Crichton ML, Shoemark A, et al. The efficacy and safety of inhaled antibiotics for the treatment of bronchiectasis in adults: a systematic review and meta-analysis. Lancet Respir Med 2019;7(10):855–69. https://doi.org/10.1016/S2213-2600(19)30185-7.
44. Sibila O, Laserna E, Shoemark E, et al. Airway bacterial load and inhaled antibiotic response in

bronchiectasis. Am J Respir Crit Care Med 2019; 200(1):33–41. https://doi.org/10.1164/rccm.201809-1651OC.

45. 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;189:975–82.
46. Murray MP, Govan JR, Doherty CJ, et al. A randomised controlled trial of nebulised gentamicin in non-cystic fibrosis bronchiectasis. Am J Respir Crit Care Med 2011;183(4):491–9. https://doi.org/10.1164/rccm.201005-0756OC.
47. Loebinger MR, Polverino E, Chalmers JD, et al. Efficacy and safety of TOBI Podhaler in *Pseudomonas aeruginosa*-infected bronchiectasis patients: the iBEST study. Eur Respir J 2021;57(1):2001451. https://doi.org/10.1183/13993003.01451-2020.
48. Chalmers JD, Cipolla D, Thompson B, et al. Changes in respiratory symptoms during 48-week treatment with ARD-3150 (inhaled liposomal ciprofloxacin) in bronchiectasis: results from the ORBIT-3 and -4 studies. Eur Respir J 2020;56(4):2000110. https://doi.org/10.1183/13993003.00110-2020.
49. Chalmers JD, Aliberti S, Filonenko A, et al. Characterization of the frequent exacerbator phenotype in bronchiectasis. Am J Respir Crit Care Med 2018; 197(11):1410–20. https://doi.org/10.1164/rccm.201711-2202OC.
50. Finch S, McDonnell MJ, Abo-Leyah H, et al. A comprehensive analysis of *Pseudomonas aeruginosa* colonisation on prognosis in adult bronchiectasis. Ann Am Thorac Soc 2015;12(11):1602–11. https://doi.org/10.1513/AnnalsATS.201506-333OC.
51. Orriols R, Hernando R, Ferrer A, et al. Eradication therapy against *Pseudomonas aeruginosa* in non-cystic fibrosis bronchiectasis. Respiration 2015; 90(4):299–305. https://doi.org/10.1159/000438490.