Chapter 14

Antibiotic treatment strategies in adults with bronchiectasis

C.S. Haworth

Summary

Antibiotics play a crucial role in the management of patients with bronchiectasis by disrupting the vicious circle of infection, inflammation and airway damage central to the pathophysiology of the condition. Antibiotic use in patients with bronchiectasis can be divided into exacerbation treatment, chronic suppressive treatment and eradication treatment.

Antibiotics administered during exacerbations are known to reduce serum C-reactive protein concentrations, sputum volume and bacterial density, as well as ameliorate symptoms. Clinical experience suggests that better outcomes are seen with higher dose/longer duration regimens.

The prescription of long-term oral antibiotics should be considered in patients requiring exacerbation treatment at least three times per year. As patients chronically infected with *Pseudomonas aeruginosa* tend to have a faster rate of lung function decline, more admissions to hospital and a worse quality of life compared with bronchiectasis patients with other microorganisms, nebulised antipseudomonal antibiotics are commonly prescribed.

Eradication antibiotics should be considered following identification of new growths of *P. aeruginosa* due to the increased morbidity associated with chronic infection.

Keywords: Antibiotics, bronchiectasis, exacerbation, intravenous, nebulised, prophylaxis

Correspondence: C.S. Haworth, Cambridge Centre for Lung Infection, Papworth Hospital, Cambridge, CB23 3RE, UK, Email charles.haworth@papworth.nhs.uk

Eur Respir Mon 2011. 52, 211–222.

European Respiratory Monograph;
ISSN: 1025-448x.
DOI: 10.1183/1025448x.10004410

Bronchiectasis is a condition characterised by irreversible dilatation of the bronchi [1] resulting from changes in the elastic and muscular components of the bronchial wall. COLE [2] proposed the vicious circle hypothesis in the 1980s to explain the pathogenesis of bronchiectasis. He suggested that an initial insult to the airway leads to bronchial wall inflammation and damage, disordered mucociliary clearance, a predisposition to chronic or recurrent infection and as a result, further airway damage. Antibiotic use in patients with bronchiectasis can be divided into

exacerbation treatment, chronic suppressive treatment and eradication treatment. Treatment of pulmonary diseases related to nontuberculous mycobacteria and fungi will be covered by other chapters in this issue.

Antibiotic treatment in exacerbations of bronchiectasis

Patients with bronchiectasis may expectorate significant volumes of mucopurulent sputum when well. It is therefore important to document stable state symptoms so that exacerbations can be accurately identified. Failure to do this can result in inappropriate antibiotic treatment.

Acute exacerbations of bronchiectasis are characterised by an increase in cough frequency, sputum volume, sputum purulence and viscosity. Patients may also complain of chest tightness, wheeze and breathlessness. Other common features include streaky haemoptysis, chest discomfort and temperatures. Symptoms usually progress over days, but patients can experience a more insidious decline over weeks or months.

There are no randomised placebo-controlled trials evaluating the effect of antibiotic treatment during exacerbations of bronchiectasis. However, antibiotics are known to reduce serum C-reactive protein, sputum inflammatory indices, sputum volume, sputum purulence and bacterial density, as well as ameliorate symptoms [3–8].

The published literature evaluating antibiotic treatment during exacerbations of bronchiectasis is heterogeneous in terms of the class of antibiotic studied, the route of administration and the sputum microbiology of the participants. However, important management principals emerge: high doses of an antibiotic are often more effective than lower doses of the same antibiotic [3]; patients with purulent sputum after antibiotic treatment have a shorter time to next exacerbation compared with patients with mucoid sputum [3]; sputum culture sensitivity results do not necessarily predict clinical response to antibiotic treatment [9]; short courses of oral antibiotics prescribed during acute exacerbations reduce airway inflammatory indices to pre-exacerbation levels, but chronic low-grade inflammation persists [4]; and clinical improvement may not be associated with significant increases in spirometry [7, 8, 10].

Initial treatment usually involves a course of oral antibiotics unless the patient is sufficiently unwell to require intravenous treatment. The optimal dose and duration of antibiotic treatment to manage bronchiectasis exacerbations is currently undefined. Clinical experience suggests that better outcomes are seen with higher dose/longer duration regimens, which presumably reflects the difficulty of achieving adequate antibiotic concentrations within the lumen of bronchiectatic airways, particularly in the context of chronic infection where bacteria are often resistant and protected by biofilms. Expert consensus is that bronchiectasis exacerbations should be treated with 14 days of antibiotics [11]. A sputum sample should be sent for culture before starting empirical antibiotic treatment and the results can influence changes in treatment if the patient is not responding.

Oral antibiotic treatment for exacerbations of bronchiectasis

Oral antibiotic choices should be guided, where possible, by previous sputum microbiology and suggestions for treatment are outlined in table 1. Empirical treatment may be with amoxicillin 500 mg *t.i.d.* or co-amoxiclav 625 mg *t.i.d.* in patients in whom β-lactamase-producing organisms are suspected. Doxycycline 100 mg *b.i.d.* is an alternative choice in the context of penicillin allergy and ciprofloxacin 750 mg *b.i.d.* should be prescribed if *Pseudomonas aeruginosa* infection is thought to be likely. Patients with a history of methicillin-resistant *Staphylococcus aureus* (MRSA) infection may be treated with rifampicin 600 mg *q.d.* and fucidin 500 mg *t.i.d.* The potential for antibiotic related complications such as *Clostridium difficile* infection need to be considered when choosing oral or *i.v.* antibiotic regimens to treat exacerbations of bronchiectasis.

Table 1. Oral antibiotic regimens commonly used to treat acute exacerbations of bronchiectasis in adults[#]

Organism	First line	Second line
Streptococcus pneumoniae	Amoxicillin 500–1000 mg *t.i.d.*[¶]	Clarithromycin 500 mg *b.i.d.* Doxycycline 100 mg *b.i.d.* Moxifloxacin 400 mg *q.d.* Trimethoprim 200 mg *b.i.d.*
Haemophilus influenzae	Amoxicillin 500–1000 mg *t.i.d.*[¶]	Doxycycline 100 mg *b.i.d.* Co-amoxiclav 625 mg *t.i.d.* Ciprofloxacin 750 mg *b.i.d.* Trimethoprim 200 mg *b.i.d.*
Moraxella catarrhalis	Co-amoxiclav 625 mg *t.i.d.*	Doxycycline 100 mg *b.i.d.* Ciprofloxacin 750 mg *b.i.d.* Clarithromycin 500 mg *b.i.d.*
Staphylococcus aureus	Flucloxacillin 500–1000 mg *q.i.d.*[¶]	Clarithromycin 500 mg *b.i.d.* Doxycycline 100 mg *b.i.d.* Co-amoxiclav 625 mg *t.i.d.* Trimethoprim 200 mg *b.i.d.* Moxifloxacin 400 mg *q.d.*
MRSA	Rifampicin 400–600 mg *q.d.*[+] and fucidin 500 mg *t.i.d.*	Trimethoprim 200 mg *b.i.d.* Doxycycline 100 mg *b.i.d.* Linezolid 600 mg *b.i.d.*
Pseudomonas aeruginosa	Ciprofloxacin 750 mg *b.i.d.*	
Coliforms	Ciprofloxacin 750 mg *b.i.d.*	Co-amoxiclav 625 mg *t.i.d.*
Stenotrophomonas maltophilia	Cotrimoxazole 960 mg *b.i.d.*	Minocycline 100 mg *b.i.d.*
Achromobacter xylosoxidans	Minocycline 100 mg *b.i.d.*	

q.d.: once daily; *b.i.d.*: twice daily; *t.i.d.*: three times daily; *q.i.d.*: four times daily; MRSA: methicillin-resistant *Staphylococcus aureus*. [#]: recommended treatment duration 10–14 days; [¶]: dose according to severity; [+]: dose according to weight.

Intravenous antibiotic treatment for exacerbations of bronchiectasis

Patients with severe exacerbations or exacerbations that fail to resolve with oral antibiotic treatment may require treatment with *i.v.* antibiotics. This usually involves admission to hospital, but some centres run community-based *i.v.* antibiotic programmes, which allow patients to have all, or a proportion, of their treatment at home. This is particularly helpful for younger patients who have educational commitments or for those that do not want to take time out from work. Patients must demonstrate that they are competent at *i.v.* drug administration before discharge and the home environment needs to be appropriate. Most centres recommend that the first dose is administered in hospital to ensure patients can infuse the antibiotic correctly and to ensure there are no adverse events. 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 nephrotoxic medicines.

Antibiotic *i.v.* 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) (fig. 1). PICCs and TIVADs are particularly useful in patients with difficult peripheral access who require frequent courses of *i.v.* treatment. However, these devices require regular flushing and potential complications include thrombosis and infection, particularly in higher risk groups such as the elderly and those with a primary or secondary immunodeficiency.

Antibiotic *i.v.* choices should be based on previous sputum microbiology results and suggested regimens are outlined in table 2. Empirical antibiotic treatment may include cefuroxime or ceftriaxone, unless patients are thought to be infected with *P. aeruginosa*. As the efficacy of β-lactam antibiotics is related to the time above the mean inhibitory concentration, once daily antibiotics may be less effective than antibiotics taken three times a day due to the potential

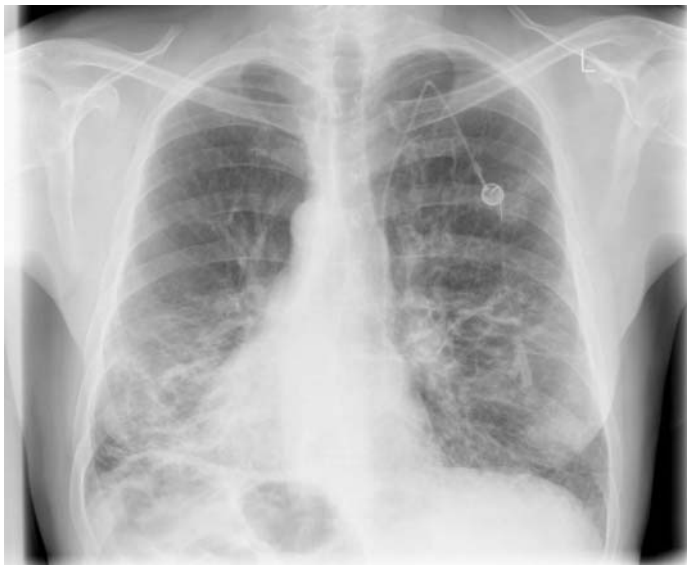

Figure 1. Chest radiograph of a male patient with primary ciliary dyskinesia, dextrocardia, severe bilateral bronchiectasis and chronic *Pseudomonas aeruginosa* infection who self-administers *i.v.* antibiotics *via* a totally implantable venous access device at home.

problem of maintaining an adequate intraluminal antibiotic concentration in the context of structural lung damage and biofilm formation.

Antibiotic *i.v.* treatment in patients infected with *P. aeruginosa*

Empirical antibiotic treatment in patients with *P. aeruginosa* may include a β-lactam, such as ceftazidime. Monotherapy may suffice in patients infected with fully sensitive *P. aeruginosa*, but in the context of a resistant organism or chronic infection where patients are likely to require repeated treatment courses in the future, many clinicians advocate dual therapy with an aminoglycoside to reduce the risk of antibiotic resistance, as well as harnessing the synergistic effects between aminoglycoside and β-lactam antibiotics [12–14]. In a study evaluating the effect of *i.v.* azlocillin + placebo *versus i.v.* azlocillin + tobramycin in patients with cystic fibrosis (CF), initial clinical outcomes were comparable, but *P. aeruginosa* density decreased more and time to next hospitalisation was significantly longer in the group receiving dual therapy [15]. These data suggest that dual antibiotic therapy is preferable in the context of chronic *P. aeruginosa* infection and the absence of significant comorbidity (such as renal dysfunction).

Table 2. Antibiotic *i.v.* regimens commonly used to treat acute exacerbations of bronchiectasis in adults[#]

Organism	First line	Second line
Streptococcus pneumoniae	Benzylpenicillin 1.2 g *q.i.d.*	Cefuroxime 1.5 g *t.i.d.* or Ceftriaxone 2 g *q.d.*
Haemophilus influenzae	Cefuroxime 1.5 g *t.i.d.* or ceftriaxone 2 g *q.d.*	Piperacillin with Tazobactam 4.5 g *t.i.d.*
Moraxella catarrhalis	Cefuroxime 1.5 g *t.i.d.* or ceftriaxone 2 g *q.d.*	Piperacillin with tazobactam 4.5 g *t.i.d.*
MRSA	Vancomycin[¶]	Teicoplanin[¶] Linezolid 600 mg *b.i.d.* Tigecycline 50 mg *b.i.d.* Fosfomycin 5 g *t.i.d.*
Pseudomonas aeruginosa	Ceftazidime 2 g *t.i.d.*[+]	Aztreonam 2 g *t.i.d.*[+] Piperacillin with tazobactam 4.5 g *t.i.d.*[+] Meropenem 1 g *t.i.d.*[+]
Coliforms	Cefuroxime 1.5 g *t.i.d.* or ceftriaxone 2 g *q.d.*	Piperacillin with tazobactam 4.5 g *t.i.d.*
Stenotrophomonas maltophilia	Cotrimoxazole 1.44 g *b.i.d.*	Tigecycline 50 mg *b.i.d.*
Achromobacter xylosoxidans	Piperacillin with tazobactam 4.5 g *t.i.d.*	Meropenem 1 g *t.i.d.*

q.d.: once daily; *b.i.d.*: twice daily; *t.i.d.*: three times daily; *q.i.d.*: four times daily; MRSA: methicillin-resistant *Staphylococcus aureus*. [#]: recommended treatment duration 10–14 days; [¶]: dose according to weight and drug levels; [+]: dual therapy with gentamicin or tobramycin may be required.

The most appropriate choice of aminoglycoside remains a matter for debate, but recent reports suggest that the risk of renal impairment, ototoxicity and vestibular damage is greater with gentamicin than tobramycin [16, 17]. While, once daily *versus* three times daily tobramycin dosing in children with CF appears to offer equivalent clinical outcomes and reduced renal toxicity [18], the most appropriate dosing regimen has not been established in adults with bronchiectasis.

The role of antibiotic sensitivity testing in patients with bronchiectasis and chronic *P. aeruginosa* infection is contentious due to hypermutation and the poor correlation between *in vitro* antibiotic sensitivity test results and clinical outcomes [19, 20]. FOWERAKER *et al.* [19] studied sputum samples from patients with CF and found an average of four *P. aeruginosa* morphotypes per sputum sample and three distinct antibiotic sensitivity profiles per morphotype. 48 colonies with varying antibiotic sensitivity profiles were cultured from one sputum sample and it was noted that susceptibility profiles of single *P. aeruginosa* isolates correlated poorly with pooled cultures (the pooled cultures underestimated levels of antibiotic resistance). FOWERAKER *et al.* [19] also showed that sensitivity results from one sputum sample tested in duplicate by eight biomedical scientists within one laboratory and by biomedical scientists in seven other laboratories did not correlate well. These data are supported by the findings of SMITH *et al.* [21], 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 CF. Furthermore, a randomised controlled trial evaluating clinical outcomes, using multiple combination bactericidal testing *versus* clinician preference, to guide *i.v.* antibiotic choices to manage CF pulmonary exacerbations showed no advantage in using the more sophisticated microbiological tests [22]. Based on the above evidence, a pragmatic approach is required when choosing antibiotic combinations for patients with bronchiectasis and chronic *P. aeruginosa* infection. It is common practice to choose two antipseudomonal antibiotics (usually a β-lactam in combination with tobramycin) to which the majority of morphotypes are sensitive. An alternative approach involves basing antibiotic choices predominantly on what has worked well for the patient in the past.

Nebulised antibiotic treatment for exacerbations of bronchiectasis

The nebulised route enables delivery of high concentrations of antibiotic to the airways and reduces the likelihood of gastrointestinal adverse events. However, airway inflammation may lead to bronchoconstriction and drug deposition may be limited by sputum plugging.

BILTON *et al.* [6] tested the effect of adding inhaled tobramycin solution to oral ciprofloxacin for treatment of bronchiectasis exacerbations in the context of *P. aeruginosa* infection. The study involved 53 adults recruited from 17 study centres in the UK and USA. There was evidence of superior microbiological efficacy in patients receiving inhaled tobramycin and ciprofloxacin compared with those receiving ciprofloxacin alone, but superior clinical efficacy was not demonstrated. Patients treated with inhaled tobramycin and ciprofloxacin were more likely to experience respiratory adverse events, in particular wheeze (50% in the inhaled tobramycin group compared with 15% in the placebo group). Although treatment emergent wheeze was not a significant cause for withdrawal from the study, it is probable that it influenced the clinical efficacy outcome data. It is also notable that patients with ciprofloxacin resistant strains of *P. aeruginosa* were excluded from the study and it is possible that the inclusion of such patients, as would occur in routine clinical practice, may have resulted in more favourable outcomes in the inhaled tobramycin-treated patients.

Antibiotic prophylaxis in adults with bronchiectasis

Antibiotics are commonly prescribed on a long-term basis in patients with bronchiectasis with a view to improving symptoms, decreasing exacerbation rates and optimising quality of life. The most likely mechanism by which antibiotics achieve these aims is by reducing bacterial load and airway inflammation. The immunomodulatory benefits of long-term macrolide antibiotics are discussed in a later chapter by SMITH *et al.* [23].

Antibiotics used on a long-term basis are usually administered orally or through a nebuliser. However, within the CF population, some centres advocate 3-monthly elective courses of *i.v.* antibiotics for patients chronically infected with *P. aeruginosa* [24]. This approach has not been taken up widely due to concerns about toxicity (particularly renal, vestibular and auditory), psychosocial well-being (disruption to family life, work and education), healthcare costs and those concerns relevant to all forms of antibiotic prophylaxis: increasing bacterial resistance and the creation of a niche for new organisms (both bacteria and fungi) [25, 26].

Oral antibiotic prophylaxis in adults with bronchiectasis

The evidence base for oral antibiotic prophylaxis in bronchiectasis dates back to the early 1950s when a number of unrandomised studies were performed [27, 28]. However, these were soon superseded by the Medical Research Council study which involved 122 subjects randomised to receive penicillin, oxytetracycline or placebo [29]. The drugs were provided as indistinguishable 0.25 g capsules and patients were asked to take two capsules four times a day on two days each week for 1 year. Outcome measures included 24-h sputum volume and the severity of cough, dyspnoea, haemoptysis and disability. Unfortunately no formal statistical analysis was performed. After 1 year, oxytetracycline treatment was associated with a reduction in sputum volume to 64% of pre-treatment levels and the purulent fraction was reduced by 50%. Treatment with oxytetracycline was also associated with fewer days off work and fewer days confined to bed. Less marked changes were evident in patients allocated to the penicillin and placebo groups. Gastrointestinal symptoms were reported by a minority of patients (five on oxytetracycline, three on penicillin and two on placebo) and one patient in the oxytetracycline and penicillin groups discontinued treatment due to antibiotic intolerance. Unfortunately, sputum microbiology data were not reported and so it is not possible to make an assessment of whether sensitivity profiles affected outcomes. 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 [30, 31]. However, the latter study also reported an increase in the isolation of *Pseudomonas* and *Proteus* species, suggesting that microbial flora of sputum may be altered by long-term antibiotic treatment.

CURRIE *et al.* [32] performed a randomised placebo-controlled trial evaluating the effect of high-dose amoxicillin in patients with bronchiectasis. 38 subjects were randomised to receive amoxicillin 3 g *b.i.d.* or placebo for 32 weeks. Assessment of overall response based on diary card data showed that a higher proportion of patients improved in the amoxicillin group (11 out of 17) compared with the placebo group (four out of 19). Patients in the amoxicillin group also spent significantly less time confined to bed and away from work compared with the placebo group. The frequency of exacerbation was similar in the two groups, but the exacerbations were less severe in the amoxicillin group than before the study was started. There was also a greater reduction in purulent sputum volume in the amoxicillin group (20% of pre-treatment volume) compared with the placebo group (88% of pre-treatment volume). One patient in the amoxicillin group withdrew from the study due to the development of rash and one patient from each group withdrew due to diarrhoea. There was a trend towards greater antibiotic resistance in patients treated with amoxicillin. No patients developed *C. difficile*-related diarrhoea.

In a 16-week open-label study of oral and nebulised amoxicillin involving 10 patients with bronchiectasis and variable sputum microbiology (predominantly *Haemophilus influenzae*), treatment was associated with reduced sputum purulence and volume, reduced sputum inflammatory indices, improvements in lung function and improved patient well-being [33]. After cessation of treatment, sputum purulence returned after a median of 2.5 months.

RAYNOR *et al.* [34] performed a retrospective case note review of 10 patients with bronchiectasis prescribed >90 days of continuous oral ciprofloxacin. Pre-treatment sputum microbiology results from nine patients showed a variety of organisms including *P. aeruginosa* (n=5), *H. influenzae* (n=3) and *Streptococcus pneumoniae* (n=1). At the end of treatment six patients had sterile sputum

cultures, of which two had previously grown *P. aeruginosa*, three *H. influenzae* and one had no pathogen. In one patient *P. aeruginosa* was replaced by *S. pneumoniae*, two patients continued to culture *P. aeruginosa* (which had become resistant to ciprofloxacin) and *S. pneumoniae* persisted in one patient. While exacerbation frequency and hospital admissions reduced with treatment, the development of ciprofloxacin-resistant strains of *P. aeruginosa* is of concern, particularly as this finding coincided with a relapse in symptoms requiring admission to hospital for *i.v.* antibiotics.

In practice, the prescription of long-term oral antibiotics is considered in patients requiring exacerbation treatment at least three times per year (or in patients with fewer exacerbations but greater associated morbidity) [11]. There may also be a lower threshold to prescribe long-term antibiotics in patients with a primary or secondary immunodeficiency. Common long-term oral antibiotic regimens are outlined in table 3. Where possible, antibiotic choices should be based on sputum microbiology data. While there is no evidence currently in favour of antibiotic rotation over single agent prophylaxis in terms of the development of antibiotic resistance and efficacy, it is important to record exacerbation rates before and after starting long-term oral antibiotics and to perform regular sputum surveillance to monitor antibiotic resistance patterns and to identify treatment emergent bacteria and fungi.

Nebulised antibiotic prophylaxis in patients with bronchiectasis

There have been a number of studies conducted using nebulised antibiotics in patients with bronchiectasis. The majority involve antipseudomonal agents, although earlier studies evaluated the use of nebulised amoxicillin in patients predominantly infected with *H. influenzae* [3, 33, 35]. While the results of the nebulised amoxicillin trials are largely positive, in practice this intervention is rarely used as high-dose oral regimens are easier and cheaper to administer.

Antipseudomonal nebulised antibiotic regimens evaluated to date include nebulised gentamicin, nebulised tobramycin, nebulised tobramycin in combination with nebulised ceftazidime and nebulised colistin. The largest published study was performed by BARKER *et al.* [36] and evaluated the microbiological efficacy and safety of inhaled tobramycin in patients with bronchiectasis infected with *P. aeruginosa*. Patients were randomly assigned to receive either tobramycin solution for inhalation (n=37) or placebo (n=37) twice daily for 4 weeks. At week 4, the tobramycin solution for inhalation group had a mean decrease in *P. aeruginosa* density of 4.5 $\log_{10}$ colony forming units per gram ($CFU \cdot g^{-1}$) of sputum compared with no change in the placebo group ($p<0.01$). Logistic regression analysis showed that decreases in $CFU \cdot g^{-1}$ of sputum were significant predictors of improved well-being. 2 weeks after cessation of the trial, *P. aeruginosa* was eradicated in 35% of the tobramycin-treated group, but was detected in all placebo patients. 62% of

Table 3. Oral antibiotic prophylaxis for adult patients with bronchiectasis based on sputum microbiology

Organism	First line	Second line
Streptococcus pneumoniae	Amoxicillin 500 mg *b.i.d.*	Clarithromycin 500 mg *b.i.d.* Doxycycline 100 mg *q.d.* Trimethoprim 200 mg *b.i.d.*
Haemophilus influenzae	Amoxicillin 500 mg *b.i.d.*	Doxycycline 100 mg *q.d.* Trimethoprim 200 mg *b.i.d.*
Moraxella catarrhalis	Amoxicillin 500 mg *b.i.d.*	Doxycycline 100 mg *q.d.* Clarithromycin 500 mg *b.i.d.*
Staphylococcus aureus	Flucloxacillin 500 mg–1 g *b.i.d.*	Clarithromycin 500 mg *b.i.d.* Doxycycline 100 mg *q.d.* Trimethoprim 200 mg *b.i.d.*
MRSA	Trimethoprim 200 mg *b.i.d.*	Doxycycline 100 mg *q.d.*
Stenotrophomonas maltophilia	Cotrimoxazole 960 mg *b.i.d.*	Minocycline 100 mg *b.i.d.*
Achromobacter xylosoxidans	Minocycline 100 mg *b.i.d.*	

q.d.: once daily; *b.i.d.*: twice daily; MRSA: methicillin-resistant *Staphylococcus aureus*.

tobramycin-treated patients showed improvement in their medical condition compared with 38% of the placebo patients (OR 2.7, 95% CI 1.1–6.9), but there was no significant change in lung function between the treatment groups. Tobramycin-resistant *P. aeruginosa* strains developed in four (11%) out of 36 of tobramycin-treated patients and one (3%) out of 32 of placebo-treated patients. Three of the four patients in the tobramycin-treated group who developed resistant *P. aeruginosa* strains showed no microbiological response and all four failed to improve clinically. More tobramycin-treated patients than placebo patients reported increased cough, breathlessness, wheezing and non-cardiac type chest pain, but the symptoms did not appear to limit therapy.

A second trial evaluating tobramycin solution for inhalation involved 41 bronchiectasis patients infected with *P. aeruginosa* and employed an open-label design consisting of three treatment cycles (14 days of drug therapy and 14 days off) [37]. During the 12-week treatment period significant improvements occurred in the pulmonary symptoms severity score and in quality of life measurements. However, tobramycin-resistant strains of *P. aeruginosa* developed in two subjects and 10 patients dropped out due to adverse events, the most common being cough, wheeze and breathlessness. Five subjects died during the study period due to the underlying disease, one during the 12-week treatment period and four during the 40-week follow-up period. None of the deaths were considered to be related to the drug treatment.

DROBNIC *et al.* [38] evaluated an alternative formulation of tobramycin in a double-blind placebo-controlled cross-over trial involving 30 patients. Patients received aerosolised tobramycin 300 mg or placebo twice daily for 6 months, with a 1-month wash out period between interventions. 20 patients completed the protocol as three patients withdrew from the study due to bronchospasm, five patients died from respiratory failure and two others dropped out (one failed to adhere to the study protocol and one relocated). The number of admissions and in-patient days reduced during the tobramycin period. There was also a decrease in *P. aeruginosa* density which persisted up until 3 months after nebulised tobramycin treatment had been stopped and there was no difference in the emergence of bacterial resistance between the two study periods. However, there was no significant difference in the number of exacerbations, antibiotic use, lung function or quality of life between the tobramycin and placebo periods.

ORRIOLS *et al.* [39] performed a 12-month study in which patients with bronchiectasis were randomised to receive nebulised ceftazidime 1 g *b.i.d.* + tobramycin 100 mg *b.i.d.* or symptomatic treatment. One out of eight patients in the nebulised antibiotic group withdrew having developed bronchospasm and one out of nine patients in the control group died. While there were significantly less admissions and in-patient days in the nebulised antibiotic group, these findings need to be interpreted with care owing to the open-label design of the study. Interestingly, there was no difference in the use of oral antibiotics or change in lung function between the two treatment groups. There was also no difference in the emergence of antibiotic resistant bacteria between the two treatment groups.

LIN *et al.* [40] performed a randomised controlled trial assessing the effect of aerosolised gentamicin 40 mg (n=16) *versus* 0.45% saline (n=15) administered twice daily for 3 days in patients with bronchiectasis. Gentamicin-treated patients showed significant reductions in sputum volume and sputum inflammatory indices (there was a significant correlation between the change in sputum volume and sputum myeloperoxidase) in conjunction with significant improvements in peak expiratory flow rate and 6-min walk distances.

MURRAY *et al.* [41] performed a longer term study evaluating the effect of nebulised gentamicin in patients with bronchiectasis. 65 patients were randomised to receive gentamicin 80 mg or 0.9% saline twice daily through a nebuliser for 12 months. Inclusion criteria included a history of chronic sputum colonisation with potentially pathogenic organisms when clinically stable. After 12 months, use of nebulised Gentamicin was associated with significant reductions in bacterial density with a 30.8% eradication rate in patients infected with *P. aeruginosa* and a 92.8% eradication rate in patients infected with other pathogens. There was reduced sputum purulence (8.7% *versus* 38.5%, $p<0.001$), greater exercise capacity (median (interquartile range) 510 (350–690) m

versus 415 (267–530) m, p=0.03), fewer exacerbations (median (interquartile range) 0 (0–1) *versus* 1.5 (1–2), p<0.001), increased time to first exacerbation (median (interquartile range) 120 (87–161) days *versus* 61 (20–122) days, p=0.02) and greater improvements in quality of life in patients treated with gentamicin. There were no differences between groups in 24-h sputum volume, forced expiratory volume in 1 second, forced vital capacity (FVC) or forced expiratory flow at 25–75% of FVC. There was no development of gentamicin-resistant isolates of *P. aeruginosa*.

Small retrospective studies have evaluated the effect of nebulised colistin in patients with bronchiectasis and *P. aeruginosa* infection [42, 43]. Owing to the retrospective nature of the studies the results need to be interpreted with care, but the data suggest that nebulised colistin has beneficial effects in this patient population in terms of exacerbation frequency, admission rates, sputum volume and lung function. An international multicentre randomised placebo controlled trial evaluating the effect of nebulised colistin (promixin) on time to next exacerbation in patients with bronchiectasis and chronic *P. aeruginosa* infection is underway and will report in the next 2 years.

Patients with bronchiectasis and *P. aeruginosa* chronic infection tend to have more severe lung disease based on physiological and computed tomography parameters, a faster rate of lung function decline, more admissions to hospital and a worse quality of life compared with patients with other microorganisms [44–48]. Thus, nebulised antibiotics are frequently prescribed for patients with bronchiectasis and chronic *P. aeruginosa* infection in order to improve well-being and prevent disease progression, consistent with CF management principals [14, 25]. Common nebulised antibiotic regimens are outlined in table 4. It is important to record exacerbation rates before and after starting long-term nebulised antibiotics and to perform regular sputum surveillance to monitor antibiotic resistance patterns and treatment emergent bacteria and fungi.

Eradicating new growths of specific organisms in patients with bronchiectasis

There are no trials to date evaluating antibiotic eradication regimens in patients with bronchiectasis. However, in clinical practice, eradication regimens are often prescribed following identification of new growths of *P. aeruginosa* due to the increased morbidity associated with chronic infection [44–48]. Some of the oral and nebulised 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 [34, 36–39, 41]. In the absence of conclusive trial data, many clinicians follow treatment protocols used in patients with CF, where early eradication therapy and the subsequent reduction in prevalence of chronic *P. aeruginosa* infection is thought to have had a major impact on survival [49]. Experience suggests that eradication of *P. aeruginosa* is less likely once the organism has converted to the mucoid form, which reinforces the need for early intervention [14]. In patients

Table 4. Nebulised antibiotic prophylaxis for adult patients with bronchiectasis chronically infected with *Pseudomonas aeruginosa*

Drug and formulation[#]	Dose	Diluent
Colistin (Colomycin)	2 MU *b.i.d.*	4 mL 0.9% sodium chloride
Colistin (Promixin)	1 MU *b.i.d.*	1 mL water for injection
Gentamicin 40 mg·mL^{-1}	80 mg *b.i.d.*	1 mL 0.9% sodium chloride
Tobramycin (Tobi)	300 mg *b.i.d.*	
Tobramycin (Bramitob)	300 mg *b.i.d.*	
Aztreonam lysine (Cayston)	75 mg *t.i.d.*	1 mL 0.17% sodium chloride
Ceftazidime	1 g *b.i.d.*	3 mL water for injection

MU: million units; *b.i.d.*: twice daily; *t.i.d.*: three times daily. [#]: unlicensed indication.

with CF and a new growth of *P. aeruginosa*, the prescription of ciprofloxacin + nebulised colistin resulted in 16% of treated patients developing chronic *P. aeruginosa* infection compared with 72% of untreated historical controls ($p<0.005$) after 3.5 years follow-up [50]. More recent data showed that >90% of patients with CF and early *P. aeruginosa* infection had negative cultures 1 month after completing a 4-week course of nebulised tobramycin (tobi 300 mg *q.i.d.*) [51]. In practice, many clinicians prescribe a 3-month course of nebulised colistin in combination with oral ciprofloxacin for patients with bronchiectasis and a new growth of *P. aeruginosa* [11, 14, 52], and offer *i.v.* therapy if this intervention fails.

Eradication regimens are also commonly instituted in patients who culture MRSA in their sputum for the first time, due to the fact that it is a resistant organism and has significant infection control implications. Oral rifampicin and fucidin with or without nebulised vancomycin is used in some centres, but treatment regimens should be based around local policies.

Future antibiotic treatment strategies

It is likely that antibiotic treatment options for patients with bronchiectasis will change significantly over the next decade. New nebulised (amikacin, aztreonam, colistin and fosfomycin in combination with tobramycin) and dry powder (ciprofloxacin, colistin and tobramycin) antibiotic formulations have been developed and may be beneficial in patients with bronchiectasis. New ways of using old antibiotics may also lead to improved outcomes. For example, due to the time-dependent antibacterial activity of β-lactam antibiotics, continuous infusions may offer superior efficacy compared with intermittent infusions [53], particularly in the context of severe structural lung damage and biofilm formation.

Conclusion

Antibiotics play a crucial role in the management of patients with bronchiectasis by disrupting the infection component of the vicious circle of infection, inflammation and airway damage central to the pathophysiology of bronchiectasis. Antibiotics can be used for treatment of exacerbations, for chronic bacterial suppression and for eradication. Antibiotic choices should be based on sputum microbiological results. Careful monitoring is required regarding microbial resistance patterns and treatment emergent bacteria/fungi, gastrointestinal adverse events (*C. difficile* infection) and antibiotic related toxicity (particularly with aminoglycosides). In the future, antibiotic options are likely to increase through the development of new nebulised and dry powder formulations.

Statement of interest

C.S. Haworth has received educational grants, speaker fees or performed consultancy work for Chiesi, Gilead, Novartis and Forest.

References

1. Reid LM. Reduction in bronchial subdivision in bronchiectasis. *Thorax* 1950; 5: 233–247.
2. Cole PJ. Inflammation: a two-edge sword – the model of bronchiectasis. *Eur J Respir Dis* 1986; 69: 6–15.
3. 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: 559–565.
4. Ip M, Shum D, Lauder I, *et al.* Effect of antibiotics on sputum inflammatory contents in acute exacerbations of bronchiectasis. *Respir Med* 1993; 87: 449–454.
5. 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 Respir J* 1999; 14: 1206–1209.
6. 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: 1503–1510.
7. Courtney JM, Kelly MG, Watt A, *et al.* Quality of life and inflammation in exacerbations of bronchiectasis. *Chron Respir Dis* 2008; 5: 161–168.

8. Murray MP, Turnball K, MacQuarrie, *et al.* Assessing response to treatment of exacerbations of bronchiectasis in adults. *Eur Respir J* 2009; 33: 312–318.
9. Stockley RA, Hill SL, Morrison HM. Effect of antibiotic treatment on sputum elastase in bronchiectatic outpatients in a stable clinical state. *Thorax* 1984; 39: 414–419.
10. Hill SL, Stockley RA. Effect of short and long term antibiotic response on lung function in bronchiectasis. *Thorax* 1986; 41: 798–800.
11. Pasteur MC, Bilton D, Hill AT. British Thoracic Society Guideline for non-CF Bronchiectasis. *Thorax* 2010; 65: Suppl. 1, 1–58.
12. Cheng K, Smyth RL, Govan JR, *et al.* Spread of a β-lactam-resistant *Pseudomonas aeruginosa* in a cystic fibrosis clinic. *Lancet* 1996; 348: 639–642.
13. Elphick HE, Tan A. Single *versus* combination intravenous antibiotic therapy for people with cystic fibrosis. *Cochrane Database Syst Rev* 2005; 2: CD002007.
14. Cystic Fibrosis Trust. Antibiotic treatment for Cystic Fibrosis. Report of the UK Cystic Fibrosis Trust Working Group. 3rd Edn. Cystic Fibrosis Trust, 2009. www.cftrust.org.uk/aboutcf/publications/consensusdoc/Antibiotic_treatment_for_Cystic_Fibrosis.pdf.
15. Smith AL, Doershuk C, Goldman D, *et al.* Comparison of a β-lactam alone *versus* β-lactam and an aminoglycoside for pulmonary exacerbation in cystic fibrosis. *J Pediatr* 1999; 134: 413–421.
16. Bertenshaw C, Watson AR, Lewis S, *et al.* Survey of acute renal failure in patients with cystic fibrosis in the UK. *Thorax* 2007; 62: 541–545.
17. 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: 532–535.
18. 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: 573–578.
19. 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: 921–927.
20. 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: 728–732.
21. 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: 1495–1502.
22. 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: 463–471.
23. Smith DJ, Chang AB, Bell SC. Anti-inflammatory therapies in bronchiectasis. *Eur Respir Mon* 2011; 52: 223–238.
24. Frederiksen B, Laang S, Koch C, *et al.* Improved survival in the Danish center-treated cystic fibrosis patients: results of aggressive treatment. *Pediatr Pulmonol* 1996; 21: 153–158.
25. Ramsey BW, Pepe MS, Quan JM, *et al.* Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. *N Engl J Med* 1999; 340: 23–30.
26. Bargon J, Dauletbaev N, Kohler B, *et al.* Prophylactic antibiotic therapy is associated with an increased prevalence of *Aspergillus* colonization in adult cystic fibrosis patients. *Respir Med* 1999; 93: 835–838.
27. Harris SM, Gomell L, Shore C, *et al.* Chloramphenicol in the control of bronchial suppuration. *Dis Chest* 1952; 21: 450–454.
28. McVay LV, Sprunt DH. Antibiotic prophylaxis in chronic respiratory disease. *Ann Intern Med* 1953; 92: 883–886.
29. 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: 255–259.
30. Cherniack NS, Vosti KL, Dowling HF, *et al.* Long-term treatment of bronchiectasis and chronic bronchitis. *Arch Intern Med* 1959; 103: 345–353.
31. 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: 329–339.
32. 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.
33. 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: 163–173.
34. Raynor 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: 149–156.
35. Stockley RA, Hill SL, Burnett D. Nebulized amoxicillin in chronic purulent bronchiectasis. *Clin Ther* 1985; 7: 593–599.
36. 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: 481–485.
37. Scheinberg P, Shore E. A pilot study of the safety and efficacy of tobramycin solution for inhalation in patients with severe bronchiectasis. *Chest* 2005; 127: 1420–1426.

38. 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: 39–44.
39. Orriols R, Roig J, Ferrer J, *et al.* Inhaled antibiotic therapy in non-cystic fibrosis patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa. Respir Med* 1999; 93: 476–480.
40. Lin H-C, Cheng H-F, Wang C-F, *et al.* Inhaled gentamicin reduces airway neutrophil activity and mucus secretion in bronchiectasis. *Am J Respir Crit Care Med* 1997; 155: 2024–2029.
41. 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: 491–499.
42. Steinfort DP, Steinfort C. Effect of long-term nebulized colistin on lung function and quality of life in patients with chronic bronchial sepsis. *Int Med J* 2007; 37: 495–498.
43. Dhar R, Anwar GA, Bourke SC, *et al.* Efficacy of nebulised colomycin in patients with non-cystic fibrosis bronchiectasis colonised with *Pseudomonas aeruginosa. Thorax* 2010; 65: 553.
44. Evans SA, Turner SM, Bosch BJ, *et al.* Lung function in bronchiectasis: the influence of *Pseudomonas aeruginosa. Eur Respir J* 1996; 9: 1601–1604.
45. 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: 1754–1760.
46. Miszkiel KA, Wells AU, Ribens M, *et al.* Effects of airway infection by *Pseudomonas aeruginosa*: a computed tomographic study. *Thorax* 1997; 52: 260–264.
47. Ho P-L, Chan K-N, Ip MSM, *et al.* The effect of *Pseudomonas aeruginosa* infection on steady-state bronchiectasis. *Chest* 1998; 114: 1594–1598.
48. 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: 1565–1572.
49. Lee TW, Brownlee KG, Denton M, *et al.* Reduction in prevalence of chronic *Pseudomonas aeruginosa* infection at a regional paediatric cystic fibrosis center. *Pediatr Pulmonol* 2004; 37: 104–110.
50. Frederiksen B, Koch C, Hoiby N. Antibiotic treatment of initial colonization with *Pseudomonas aeruginosa* postpones chronic infection and prevents deterioration of pulmonary function in cystic fibrosis. *Pediatr Pulmonol* 1997; 23: 330–335.
51. Ratjen F, Munck A, Kho P, *et al.* Treatment of early *Pseudomonas aeruginosa* in patients with cystic fibrosis: the ELITE trial. *Thorax* 2010; 65: 286–291.
52. Wood DM, Smyth AR. Antibiotic strategies for eradicating *Pseudomonas aeruginosa* in people with cystic fibrosis. *Cochrane Database Syst Rev* 2006; 1: CD004197.
53. Hubert D, Le Roux E, Lavrut T, *et al.* Continuous *versus* intermittent infusions of ceftazidime for treating exacerbations of cystic fibrosis. *Antimicrob Agents Chemother* 2009; 53: 3650–3656.