Bronchiectasis: Treatment decisions for pulmonary exacerbations and their prevention

SCOTT C. BELL,1,2,3 © JOSEPH S. ELBORN4,5,6 AND CATHERINE A. BYRNES7,8

INTRODUCTION

Interest in bronchiectasis has increased over the past two decades, as shown by the establishment of disease-specific registries in several countries, the publication of management guidelines and a growing number of clinical trials to address evidence gaps for treatment decisions. This review considers the evidence for defining and treating pulmonary exacerbations, the approaches for eradication of newly identified airway pathogens and the methods to prevent exacerbations through long-term treatments from a pragmatic practice-based perspective. Areas for future studies are also explored.

Key words: bacterial infection, bronchiectasis, eradication, Pseudomonas aeruginosa, pulmonary exacerbations.

ABSTRACT

Interest in bronchiectasis has increased over the past two decades, as shown by the establishment of disease-specific registries in several countries, the publication of management guidelines and a growing number of clinical trials to address evidence gaps for treatment decisions. This review considers the evidence for defining and treating pulmonary exacerbations, the approaches for eradication of newly identified airway pathogens and the methods to prevent exacerbations through long-term treatments from a pragmatic practice-based perspective. Areas for future studies are also explored.

INTRODUCTION

There has been increasing interest in the field of bronchiectasis over the past two decades. The term orphan disease should now be considered redundant for this condition.1–3 Many studies have reported increasing prevalence, particularly in indigenous populations, and have highlighted the limited evidence base for therapeutic decision-making.4,5 Bronchiectasis-specific registries have been launched in the past 10 years including the EMBARC European Bronchiectasis Registry (https://www.bronchiectasis.eu/registry), the US Bronchietasis Research Registry (https://www.copdfoundation.org/Research/Bronchietasis-Research-Registry/Learn-More.aspx) and the Australian Bronchiectasis Registry (https://lungfoundation.com.au/health-professionals/bronchiectasis-registry/, accessed 20 July 2018) established to enhance understanding of the demographics, risk factors, natural history and impact on health-related quality of life (HRQoL).

Initial reports from the European and US registries were published in the past 2 years6–8 and these registries are now combined to form an alliance, the International Bronchiectasis Network. They have already provided an opportunity for patients with bronchiectasis to be identified as potential participants in clinical trials to obtain stronger evidence for bronchiectasis management.

Until such evidence is available, clinicians are reliant on guidelines to support clinical decision-making. The first national guideline from the UK was published in 2010, with now a number of national and one international guideline published; from Spain (initially in 2008 and revised in 2018); from Australia and New Zealand (initially 2010, revised 2015, indigenous guideline 2008); from Saudi Arabia (2017); and the European Guidelines (2017).9–16 Of note the strength of evidence to support decision-making is limited for most recommendations within these guidelines.15 Further research in all areas is urgently required. However, it is concerning that many recent clinical trials particularly of inhaled antibiotics have not achieved their primary endpoint(s).17–20 This may in part relate to several factors including the aetiology of bronchiectasis being heterogeneous, varying disease severity and age of presentation ranging from young children to the elderly. The impact of therapeutic interventions may differ amongst those with bronchiectasis from different causes.

Using the search terms ‘bronchiectasis’ and ‘clinical trials’ (PubMed), 53 publications were identified...
between 2003 and 2008, 77 publications between 2008 and 2013 and 126 publications between 2013 and 2018. Yet, in the past 5 years, there have been <20 randomized-controlled trials (RCT) published, 5 clinical trial protocols and only 2 RCT have involved children.

Chronic airway infection is routinely described (particularly with common pathogens including Haemophilus influenzae infection and Pseudomonas aeruginosa infection)\(^{21,22}\) and pulmonary exacerbations are frequent.\(^{23}\) Recent data from the EMBARC Bronchiectasis Registry has demonstrated that ~50% of patients had two or more exacerbations annually and one in three required hospitalization.\(^{24}\) It is well known that pulmonary exacerbations are associated with increased local airway and systemic inflammatory response and progressive disease.\(^{24-28}\) The severity and frequency of exacerbations adversely impact daily symptoms, HRQoL, lung function decline and mortality.\(^{29-34}\)

The purpose of this review is to address three specific areas in treating adults and children with bronchiectasis:

1. Definitions and management of pulmonary exacerbations;
2. Approaches to eradication of infection;
3. Long-term treatment aimed at reducing pulmonary exacerbations.

Under each of these three areas, we have proposed five questions and provide a synthesis of the evidence to support decision-making for the clinician with a patient with bronchiectasis in the clinic setting. We suggest pragmatic approaches based on the current published evidence and guidelines.

DEFINITION AND TREATMENT OF EXACERBATIONS IN BRONCHIECTASIS

How important is the effect of exacerbations on outcomes?

Exacerbations of chronic lung conditions such as COPD and cystic fibrosis (CF) are linked with infection and associated with poor outcomes.\(^{35,36}\) In bronchiectasis, increased pulmonary exacerbation frequency was associated with reduced forced expiratory volume in 1 s (FEV\(_1\)), increased severity of lung disease on CT scan and chronic infection with \(P.\) aeruginosa and \(H.\) influenzae. High levels of sputum neutrophil elastase were also associated with exacerbations suggesting that airway inflammation may also be an important factor.\(^{24}\)

In studies utilizing the Bronchiectasis Severity Score\(^{10}\) and the modified FACED plus exacerbations (E-FACED) score,\(^{37}\) the strongest predictor of future exacerbations was previous severe exacerbations with these scores used to successfully predict future morbidity. Prior hospitalization was also an independent predictor of mortality.\(^{30}\) A study to determine a ‘Frequent Exacerbator Phenotype’ from adults with bronchiectasis found that using 1 year as a baseline the incident rate ratio of future exacerbations over the next years was estimated at 1.73 for one exacerbation per year at baseline, 3.14 for two exacerbations and 5.97 for those with >3 exacerbations.\(^{23}\)

In children, longitudinal monitoring of lung function for 3–5 years following diagnosis of bronchiectasis demonstrated that while the overall cohort improved, a subgroup did not and this was associated with increased numbers of exacerbations (>2 per year).\(^{38,39}\)

In other studies, an annual reduction of FEV\(_1\) between −0.9% and −1.9% predicted over a minimum follow-up of 5 years was recorded, despite treatment, with greater reductions in those with chronic \(H.\) influenzae infection, which itself is associated with more frequent exacerbations.\(^{40,41}\) In CF and primary ciliary dyskinesia, single exacerbation events are associated with a failure to return to their baseline FEV\(_1\) by 3 months in ~25% of children.\(^{42,43}\) In children with bronchiectasis, for each hospitalized exacerbation, the FEV\(_1\) decreased by 1.95%\(^{39}\) and a significant worsening in parent-specific HRQoL scores.\(^{45}\)

Therefore, there is a reasonable evidence base that treatment and, even more importantly, prevention of exacerbations will improve short- and long-term health outcomes in this population.

What is an exacerbation? Do definitions help?

While exacerbations are considered to occur with a change in, or development of new, symptoms, a standard definition has been difficult to ascertain with some studies giving weight to differing parameters, or major and minor criteria, with the majority also requiring that the episode received antibiotic treatment. A recent systematic review identified 50 trials with 20 different definitions.\(^{46}\) This international consensus of experienced clinicians proposed that the definition includes: (i) a deterioration in three or more of the following key symptoms for at least 48 h: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis and (ii) a clinician determines that a change in bronchiectasis treatment is required. While this definition will be of value in clinical practice, the authors emphasize that it is a definition for research with a likely high specificity and with a bias towards more severe exacerbations. Individual patients may not reach these criteria or have additional symptoms not detailed within the definition but would still be considered to have an exacerbation requiring treatment.

Notably, measurements of lung function were not included in the definition as they are rarely helpful in confirming an episode of exacerbation in patients with bronchiectasis. In the consensus process, neither laboratory findings nor chest X-ray changes reached a sufficient threshold of support to be included.\(^{46}\) It is recognized that the ‘change of treatment’ will most likely be the initiation of antibiotics (oral, systemic or inhaled), but other possible changes could be the commencement of oral corticosteroids, mucolytics or change in airway clearance technique.

Generally, clinical trials in children have adopted similar definitions as for adults,\(^{47}\) although haemoptysis is rare and productive sounding (wet) cough is more common than sputum production. A review of 81 exacerbations in children with the purpose of defining an episode reported that wet cough or cough severity
(score ≥ 2) were the best predictors. Sputum colour, dyspnoea, haemoptysis, new clinical signs on chest examination or chest pain were considered minor criteria. The addition of particular laboratory measures (C-reactive protein (CRP), amyloid and IL6) improved the specificity and the positive predictive value of the definition—but these are not readily clinically available.48

Currently, there are no laboratory biomarkers that have been validated for bronchiectasis and how best to assess clinical status and response to treatment is poorly understood. Many clinicians managing adults with bronchiectasis use CRP as a measure of systemic inflammatory response to support decision-making on whether to initiate antibiotics and as a marker of treatment response in patients with bronchiectasis. Potential biomarkers of promise in the research setting include high-sensitivity CRP,49 neutrophil elastase24 and various pro-inflammatory cytokines.50,51

What are the optimal drugs, doses and duration? When should i.v. antibiotics be used?

It is a usual practice to initiate antibiotic treatment with some knowledge of the likely organism causing symptoms at that time. In the majority of patients with bronchiectasis, this will be H. influenzae, Moraxella catarrhalis or P. aeruginosa. Staphylococcus aureus or methicillin-resistant S. aureus (MRSA) can also be present although there is less certainty as to the impact these organisms have.52 Non-tuberculosis mycobacterium (NTM) is also increasingly described in 5–10% of patients whether because of increased awareness, increased surveillance or a true increase.53,54 In children, the most common infecting organisms are H. influenza, M. catarrhalis and Streptococcus pneumoniae. P. aeruginosa is much less common and seen predominantly in older children with severe disease, or younger children with co-morbidities of aspiration, or who have long-term tracheostomies.48,55

While the types of organisms found worldwide are similar, exact prevalence can vary according to age, region, ethnicity, referral centre, underlying cause of bronchiectasis, clinical state and recent antibiotic use.4,21,52 There will also be variation depending on sample site, sample adequacy and culture methods. Information on the current infecting organism will usually not be available until sputum culture and organisms are identified which will be 3–5 days after the sample has been processed. A knowledge of prior microorganisms is therefore very helpful in making a decision on which antibiotic is likely to be most useful. Regular sputum culture when patients are stable is therefore valuable.56

Sequencing the 16S ribosomal RNA genes in adults revealed greater bacterial diversity within sputum than detected by culture.56,57 In a study of the respiratory microbiome in children, the profile of those with CF, protracted bacterial bronchitis or bronchiectasis had more similarity between these groups than when compared to adults with CF or bronchiectasis.56 However, at this stage, airway microbiota determination is a research rather than a clinical tool.

The guidelines suggest empirical antibiotic choices predominantly divided into whether directed against P. aeruginosa or other organisms.53–55 Most exacerbations can be managed with oral antibiotics but if symptoms are moderate/severe or repeated oral therapy has not led to resolution or the individual is physiologically compromised or has co-morbidities, then an intravenous (i.v.) course of antibiotics may be warranted. For P. aeruginosa, oral oxyquinolone (ciprofloxacin) is the recommendation with a beta-lactam antibiotic (e.g. ceftazidime) with or without tobramycin indicated for i.v. treatment amoxycillin-clavulanic acid, doxycycline (>8 years old), oral second-generation cephalosporins and sulphonmethoxazole/trimetoprim will cover H. influenzae and M. catarrhalis. Where S. aureus is likely to be the predominant pathogen, sulphonmethoxazole/trimetoprim or doxycycline may be effective as these antibiotics usually have anti-MRSA activity (depending on the local susceptibility patterns).

For i.v. treatment, usually a broad-spectrum antibiotic such as a third-generation cephalosporin is used. Antibiotic therapy should be in line with local guidelines for respiratory infection and discussed with the infection team if deviations from local guidelines are required.

The duration of either oral or i.v. antibiotics has not been systematically studied in bronchiectasis. The practice of using 14 days has been extrapolated from CF practice, without definitive evidence in this population either, and is recommended in the guidelines.53,54 The European Respiratory Society (ERS) guidelines systematically reviewed the literature comparing shorter (<14 days) versus longer (14–21 days) treatment.13 In one study only, outcomes were similar at 7 and 14 days.59 However, as most studies had used 14 days and shown good outcomes, in the face of lack of evidence to the contrary, this remained the recommendation in this guideline. There are currently studies underway in patients with CF to determine the optimal length of treatment and similar studies may be valuable in bronchiectasis.

What non-antibiotic therapies should be considered for exacerbations?

There are no systematic studies to determine if adjunctive therapies are important in treating exacerbations.

Airway clearance

A regular programme of airway clearance has been associated with reduced symptoms of cough and improved quality of life (QoL)50,51 and proven more effective than no treatment.52 Only one study compared techniques during acute exacerbations56; however, chest physiotherapy by different techniques led to improvement in cough-related HRQoL even when used for a short period.63 As most exacerbations are associated with an increase in cough and sputum, it is plausible that an increase in the frequency and perhaps change of technique of airways clearance may benefit.

Corticosteroids

In patients admitted to hospital with an exacerbation of bronchiectasis, the use of systemic steroids was
associated with a threefold increased risk of mortality. 
A recent review determined no studies on the use of inhaled corticosteroids with acute exacerbations. However, a small study in children looked at withdrawing inhaled corticosteroids over 12 weeks resulting in increased bronchial hyper-reactivity and a decrease in neutrophil apoptosis but no change in sputum inflammatory markers. In adults, inhaled corticosteroids did improve HRQoL and reduce symptoms in those in ‘steady-state’ bronchiectasis. The appropriate use of steroids in bronchiectasis is complicated by the overlap of COPD and asthma in a significant number of patients.

**Mucolytics.** Only one study compared the mucolytic bromhexine against placebo showing that it improved ability to expectorate mucus during an exacerbation. No other studies have looked at use during exacerbations. Single doses of nebulized hypertonic saline increased expectorated sputum weight. Studies comparing hypertonic saline with normal saline have conflicting results and all are during time of usual care. Inhaled mannitol has been shown to be effective in prolonging time to first exacerbation and improving HRQoL but again not studied specifically during an exacerbation.

**Other.** Exacerbations are frequently associated with weight loss and attention should be given to energy intake. In adults, particularly older patients, other comorbidities may also be important to consider and drug side effects and drug–drug interactions should be considered.

**What do you do if the patient is not improving?**

Failure to respond to antibiotic therapy for a pulmonary exacerbation may be due to a number of factors including exacerbations caused by viral infections, fungal airway complications and other medical comorbidities and coexistent psychosocial stressors, anxiety and depression. These factors should be considered in the patient who is responding suboptimally to therapy.

Changing antibiotics is a frequent response when there is a failure to improve and can be modified once susceptibility profiles are known, although in vitro antibiotic susceptibility testing does not always predict therapeutic outcome. One study added inhaled tobramycin to 2 weeks of oral ciprofloxacin during acute treatment but while this reduced bacterial load it did not lead to improved clinical outcomes and lead to emergent wheeze in 50% of participants. New bacterial pathogens should be looked for and in children the difficulty of getting adequate lower airway samples means a bronchoalveolar lavage may be needed. In more severe patients, a failed response may be associated with a raised CRP and white cell count. In addition, viruses have been identified in 49% of adults at the time of exacerbation compared to 19% when stable and in 9% of patients during a winter season compared to 33% during summer.

Careful attention should be given to hypoxaemia and/or hypercapnia. Other causes of complications such as a pneumothorax or haemoptysis should be investigated. Co-morbidities such as coronary artery disease, cardiac failure or diabetes should have treatment optimized as these may contribute to the symptoms.

**ERADICATION TREATMENT IN BRONCHIECTASIS**

**In the clinically stable patient with bronchiectasis, should Pseudomonas eradication at its first isolation be considered?**

Published guidelines recommend antibiotic treatment of initial isolates of *P. aeruginosa*. Whilst eradication approaches are well established in children with CF and more recently adults with CF, this approach is based on non-controlled, non-randomized or observational clinical studies in patients with bronchiectasis.

Four recent studies specifically address the impact of eradication of *P. aeruginosa* infection. The studies from centres in Spain and the UK ranged from 30 to 64 participants and involved a range of regimens and associated with eradication of ~50–60% at ~6–12 months after completion of therapy (Table 1). It is however not clear from longitudinal studies how many patients spontaneously clear *P. aeruginosa* over time. Additionally, studies examining a range of RCT of inhaled antibiotics (tobramycin, gentamicin, ciprofloxacin; aztreonam) demonstrate eradication of *P. aeruginosa* as a secondary endpoint of the clinical trial between ~30% and 60%.

Whilst further high-quality studies are required, evidence to date supports antibiotic therapy to attempt to eradicate *P. aeruginosa* to avoid the development of chronic infection, although relapse rates in the first 6–12 months occur in a proportion of patients. A study from Belfast, UK, demonstrated success rates of eradication of 52% at 6 months, and of those ~30% will relapse by 12 months.

**What is the best regimen for *P. aeruginosa* eradication?**

There are limited data to support the choice of regimen for *P. aeruginosa* eradication. No RCT have been undertaken to address this question. Guidelines vary in the recommended approaches (drug choice, duration and combinations) from oral ciprofloxacin with or without an inhaled antibiotic (tobramycin or colistin) which may be continued for up to 12 months. The role of i.v. antibiotics is less clear but also recommended if further treatment is required. The recently published ERS bronchiectasis guidelines provide three alternative eradication protocols, based on the published uncontrolled studies (Fig. 1).

When faced with a patient with a newly identified *P. aeruginosa* culture, these options should be considered in parallel with current clinical status of the patient (stable vs recent decline), time since isolate...
<table>
<thead>
<tr>
<th>Study</th>
<th>Population (#)</th>
<th>Age (years) — mean (SD)</th>
<th>FEV₁ % predicted — mean (SD)</th>
<th>Study design</th>
<th>Oral and inhaled AB</th>
<th>Intervention (IVAB)</th>
<th>Short-term outcome¹</th>
<th>Long-term outcome²</th>
<th>Other outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>White (2012)⁷⁹</td>
<td>30</td>
<td>62.2 (17.7)</td>
<td>62.1 (23.3)</td>
<td>Observational</td>
<td>Cipro only (2 weeks)</td>
<td>IVAB (2 weeks)</td>
<td>24/30 (80%)</td>
<td>13/24 (median 14 months)</td>
<td>AB use no ΔFEV₁</td>
</tr>
<tr>
<td>Orriols (2015)⁷⁷</td>
<td>35</td>
<td>69.4 (2.1)</td>
<td>—</td>
<td>Single blind</td>
<td>Tobramycin (300 mg) vs 0.9% NS — 3 months Rx</td>
<td>IVAB (2 weeks)</td>
<td>91% at 1 month (76% for NS)</td>
<td>54% at 15 months (29% for NS)</td>
<td>Bronchospasm 5 withdrew &lt;1 month of tobra no ↑ in AMR</td>
</tr>
<tr>
<td>Vallieres (2017)⁷⁸</td>
<td>64</td>
<td>64.0 (1.6)</td>
<td>1.70 ± 0.15 L</td>
<td>Observational</td>
<td>Colistin (3 months) (1) plus Cipro (≤3 weeks (8) or &gt;3 weeks (27)) or IVAB (2 weeks) (13) or all (5) OR Cipro (6), IVAB (2), both (2)</td>
<td>IVAB (13)</td>
<td>33/64 (52%) at 6 months</td>
<td>23/33 (at ≥1 year) Eradication more common in AZM Rx patients (75% vs 47%, P = 0.04)</td>
<td></td>
</tr>
<tr>
<td>Suarez-Cuartin (2016)⁷⁷</td>
<td>38</td>
<td>N/K</td>
<td>N/K</td>
<td>Observational</td>
<td>Cipro (2 weeks) plus Colistin (3 months) (38)</td>
<td>IVAB (2 weeks)</td>
<td>53% (negative P. aeruginosa at 3 months and 1 year)</td>
<td>Rate of eradication when + for anti-PA IgG AB</td>
<td></td>
</tr>
</tbody>
</table>

¹Short-term eradication (at completion of eradication treatment or 3 months).
²Long-term eradication (at 6–12+ months).
³In nine patients, colistin continued after eradication.
⁴Δ, change; AB, antibody; AMR, antimicrobial resistance; anti-PA IgG AB, anti-P. aeruginosa IgG antibodies; AZM, azithromycin; FEV₁, forced expiratory volume in 1 s; IVAB, i.v. antibiotics; Rx, treatment.
detected, assessment of patients’ level of engagement in a complex regimen and availability of specific antibiotics. For example, in the recently published Spanish guidelines, initial treatment with ciprofloxacin 750 mg/12 h for 3 weeks is recommended. An inhaled antibiotic for 3 months can be added if the patient is unable to use ciprofloxacin (intolerance or allergy), where the patient has evidence of severe bronchiectasis and/or is immunosuppressed. However, in CF, inhaled treatment seems to be more important than oral ciprofloxacin for *P. aeruginosa* eradication. If the initial *P. aeruginosa* isolates coincide with a pulmonary exacerbation, admission and a course of 2 weeks of i.v. antibiotics are recommended.

Options to consider if *P. aeruginosa* recurs within 1 year include re-treatment with ciprofloxacin and an inhaled antibiotic (same or alternative antibiotic to that prescribed in the initial therapy) or combination of i.v. antibiotics with concurrent inhaled antibiotic.

A key factor in appraising the effectiveness of therapy is sputum surveillance for clearance of *P. aeruginosa* (during, at completion and in follow-up).

**Should eradication be considered for other bacteria (e.g. *S. aureus*, *H. influenzae*, *S. pneumoniae* and MRSA) and be treated in a clinically stable person with bronchiectasis?**

Most evidence to date highlights that *P. aeruginosa* is associated with poorer clinical outcomes (e.g. increased mortality, increased pulmonary exacerbations and increased pulmonary function decline). Bacterial infection with non-Pseudomonal bacteria is associated with pulmonary exacerbations (both numbers and severity), therefore the likely impact of attempting to eradicate such infections is less clear.

Chronic bacterial infection, particularly *H. influenzae*, is associated with poorer outcomes in children with bronchiectasis. Attempted eradication in such cases may be important; however, there are no data to date to support decision-making. The systematic review examining the role of inhaled antibiotics (six trials) for patients with bronchiectasis showed no difference in the impact of *P. aeruginosa* eradication when compared with any bacteria. One potential exception is that of managing early MRSA infection—the British Thoracic Society guidelines recommend attempted eradication of newly acquired infection for children. Whilst there are no RCT to support antibiotic selection, duration or risk-benefit in bronchiectasis, rationale appears to be linked to the potential to cause healthcare-acquired infections. Further studies are required to determine the impact of eradication of non-Pseudomonal bacteria on the natural history of bronchiectasis.

**Does the prescription of frequent and/or long-term antibiotics to prevent pulmonary exacerbations increase the risk of *P. aeruginosa* and other Gram-negative non-fermenting bacteria acquisition?**

Selective pressure of broad-spectrum antibiotic use is well established. Persistent *H. influenzae* and *P. aeruginosa* are clearly associated with the frequency of pulmonary exacerbations, although data to support the intensive use of antibiotics to treat non-Pseudomonal pathogens are limited in bronchiectasis.
Table 2  Double-blind, placebo-containing randomized-controlled trials of inhaled antibiotics in non-cystic fibrosis bronchiectasis

<table>
<thead>
<tr>
<th>Author, year, sites</th>
<th>Numbers, age, baseline exacerbations/year</th>
<th>Antibiotic, dose and duration</th>
<th>Main pathogens at baseline</th>
<th>Benefits of inhaled antibiotics vs placebo</th>
<th>Adverse effects of antibiotic vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barker, 2000&lt;sup&gt;30&lt;/sup&gt; Single centre United States</td>
<td>74 Adults Mean (SD) ages, years: 66.6 (13.0) 63.2 (13.5) placebo</td>
<td>Tobramycin solution for inhalation (n = 37) 300 mg b.d. via jet nebulizer</td>
<td><em>Pseudomonas aeruginosa</em> 100%</td>
<td>Reduced sputum <em>P. aeruginosa</em> load by 4.54 log&lt;sub&gt;10&lt;/sub&gt; cfu/g at 4 weeks (P &lt; 0.01) and eradicated in 35%. No change in placebo group</td>
<td>Dyspnoea (32% vs 8%), chest pain (19% vs 0%), wheezing (16% vs 0%); all P &lt; 0.01</td>
</tr>
<tr>
<td>Drobnic, 2005&lt;sup&gt;19&lt;/sup&gt; Single centre Spain</td>
<td>30 Adults 20 completed Mean (range) age, years: 64.5 (38–75) Recent exacerbation treated with antibiotics</td>
<td>Tobramycin injection solution (n = 30) 300 mg b.d. via jet nebulizer</td>
<td><em>P. aeruginosa</em> 100%</td>
<td>During treatment limb reduced number (0.15 vs 0.75 per patient, P = 0.04) and length (2.05 vs 12.65 patient-days, P = 0.047) of hospitalizations and also the sputum load of <em>P. aeruginosa</em> by 1–2 log&lt;sub&gt;10&lt;/sub&gt; cfu/mL</td>
<td>10% Withdraw due to bronchospasm, one other continued despite wheezing during active treatment and 4/5 died during tobramycin limb</td>
</tr>
<tr>
<td>Murray, 2011&lt;sup&gt;82&lt;/sup&gt; Single centre Scotland†</td>
<td>65 Adults Median (IQR) ages, years: 58 (53,67) 64 (56, 69) placebo</td>
<td>Gentamicin injectable solution (n = 32) 80 mg b.d. via jet nebulizer</td>
<td><em>Haemophilus influenzae</em> 46% <em>P. aeruginosa</em> 42% <em>Staphylococcus aureus</em> 5% <em>S. pneumoniae</em> 2%</td>
<td>Fewer exacerbations (median: 0 vs 1.5) involving 33% vs 80% patients (P &lt; 0.001) Median time to first exacerbation 120 vs 61.5 days (P = 0.02) Improved cough scores and less sputum purulence (9% vs 39%; P &lt; 0.05) Lower sputum bacterial density (log&lt;sub&gt;10&lt;/sub&gt; 2.96 vs 7.67 cfu/mL, P &lt; 0.001) Eradication rates: <em>P. aeruginosa</em> 31%; other bacterial pathogens 93%</td>
<td>7/32 (22%) Reported bronchospasm needing bronchodilator treatment, 2 of whom withdrew No gentamicin resistance reported All benefits disappeared within 3 months of stopping the trial</td>
</tr>
<tr>
<td>Serisier, 2013&lt;sup&gt;83&lt;/sup&gt; 11 sites Australia and New Zealand</td>
<td>42 Adults Mean (SD) ages, years: 70 (5.6) 59.5 (13.2) placebo</td>
<td>Active drug (n = 22) mixture of liposomal ciprofloxacin 150 mg and free ciprofloxacin 60 mg once daily via jet nebulizer</td>
<td><em>P. aeruginosa</em> 100%</td>
<td>Fewer patients had antibiotics for exacerbations (40% vs 77%, OR: 0.2, 95% CI: 0.04, 0.89). Median time to first exacerbation 134 vs 58 days (P = 0.06) Well tolerated without bronchodilator medication Less respiratory adverse events in treatment group (32% vs 65%), although</td>
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</table>
Two non-culture microbiome studies have reported interesting results. Patients with bronchiectasis on long-term erythromycin had evidence of changes in the composition of respiratory microbiota when exposed to macrolides. Specifically, patients without *P. aeruginosa* infection had lower rates of *H. influenzae* detected and increased rates of macrolide-tolerant pathogens including *P. aeruginosa*. However, this did not result in a change in pulmonary exacerbation rates. In another hospital-based cohort, the structure of the airway microbiota was highly specific to an individual, and was generally stable over 6 months of study despite changes in the clinical status and antibiotic usage for an individual patient.

Further studies of microbiological risk factors (using standard bacteriological culture and molecular microbiome studies) to better understand the impact of broad-spectrum and long-term antimicrobials on the establishment of more antibiotic resistant pathogens are needed.

### How to monitor if eradication has been successful in an individual patient?

Sputum bacteriological analysis is the usual approach to identify airway pathogens. Timing and frequency of sputum culture vary in the clinical care of patients ranging from taken at each outpatient assessment, during pulmonary exacerbations or when sputum is purulent, and even annual basis only. More invasive approaches (e.g. sputum induction and bronchoscopy) should be considered for the patient who is deteriorating but unable to spontaneously expectorate sputum or does not stabilize after attempted eradication.

There are no guidelines to assess efficacy of eradication therapy, although studies of the impact of...
### Table 3: Double-blind, placebo-containing randomized-controlled trials of long-term macrolide antibiotics in non-cystic fibrosis bronchiectasis

<table>
<thead>
<tr>
<th>Author, year, sites</th>
<th>Numbers, age, baseline exacerbations/year</th>
<th>Antibiotic, dose and duration</th>
<th>Main pathogens at baseline</th>
<th>Benefits of macrolides vs placebo</th>
<th>Adverse effects of macrolides vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koh, 1997109</td>
<td>25 Children (Mean (SD) age, years: 13.1 (2.6))</td>
<td>Roxithromycin (n = 13) 4 mg/kg b.d. 12 weeks Placebo (n = 12)</td>
<td>NR</td>
<td>Less airway hyper-responsiveness (P &lt; 0.01) and sputum purulence (P &lt; 0.01)</td>
<td>NR</td>
</tr>
<tr>
<td>Tsang, 1999110</td>
<td>21 Adults (Mean (SD) ages, years: 50 (15) erythromycin 59 (16) years placebo Exacerbations, NR</td>
<td>Erythromycin (n = 11) 500 mg b.d. 8 weeks Placebo (n = 10)</td>
<td>Sputum culture Pseudomonas aeruginosa 76% Haemophilus influenzae 14%</td>
<td>Improved lung function (FEV₁ by 11%; P &lt; 0.05) and reduced 24 h sputum volumes (P &lt; 0.05)</td>
<td>Rash in one patient</td>
</tr>
<tr>
<td>Wong, 2012108</td>
<td>141 Adults (Mean (SD) ages, years: 60.9 (13.6) azithromycin (EMBRACE) 59.0 (13.3) placebo Exacerbations, ≥1/year</td>
<td>Azithromycin (n = 71) 500 mg 3-days/week 6 months trial + 6 months follow-up Placebo (n = 70)</td>
<td>Sputum culture H. influenzae 28% P. aeruginosa 12% M. catarrhalis 4%</td>
<td>Fewer exacerbations (0.59 vs 1.57 per patient at 6 months; 62% reduction; P &lt; 0.001) and longer median time to next exacerbation (239 vs 85 days; P &lt; 0.001) over 12 months</td>
<td>GI symptoms 27% vs 13% (P = 0.005), one in each group discontinued Sputum microbiology profile stable, macrolide resistance testing not done systematically</td>
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<tr>
<td>Altenburg, 2013106</td>
<td>83 Adults (Mean (SD) ages, years: 69.9 (12.3) azithromycin (BAT) 64.6 (9.1) placebo Exacerbations, ≥3/year</td>
<td>Azithromycin (n = 43) 250 mg daily 12 months Placebo (n = 40)</td>
<td>Sputum culture H. influenzae 27% Staphylococcus aureus 16% P. aeruginosa 14%</td>
<td>Fewer exacerbations (median 0 vs 2; P &lt; 0.001), less patients having ≥1 exacerbation (47% vs 80%) and longer time to next exacerbation (HR: 0.29; 95% CI: 0.16, 0.51).</td>
<td>GI symptoms 40% vs 5%, mainly diarrhea, RR 8.4 (95% CI 1.1, 63) Sputum microbiology profile stable, but 53/60 pathogens (88%) from 20 azithromycin patients and 29/112 (26%) from 22 placebo patients were macrolide resistant (P &lt; 0.001)</td>
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<tr>
<td>Serisier, 2013107</td>
<td>117 (Mean (SD) ages, years: 61.1 (10.5) erythromycin (BLESS) 63.5 (9.5) placebo Exacerbations, ≥2/year needing i.v. antibiotics)</td>
<td>Erythromycin (n = 58) 250 mg b.d. 48 weeks Placebo (n = 59)</td>
<td>Sputum culture P. aeruginosa 35% H. influenzae 21%</td>
<td>Fewer exacerbations (1.29 vs 1.97/ patient/year; IRR: 0.57, 95% CI: 0.42, 0.77). Decreased 24 h sputum weight (median difference with placebo of 4.3 g; P = 0.01) and slower lung function decline (mean difference of % predicted FEV₁ with placebo 2.2%, P = 0.04)</td>
<td>Well tolerated, one patient taking erythromycin left trial with prolonged QTc interval, another taking placebo discontinued due to nausea No emergence of new sputum pathogens Increased proportions of macrolide-resistant oral streptococci (median change 28% vs 0.04%, P &lt; 0.001)</td>
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Antibiotics in bronchiectasis have reported pathogen eradication at the end of clinical trials (where eradication was a secondary endpoint), at next clinic review, at 3 and 12 months of follow-up and where no Pseudomonas was cultured in three sputum samples over 6 months after eradication. It would be pragmatic to assess sputum culture (at least once) at the next clinic appointment after antibiotics are completed and to assess regularly in the year following. The Spanish guidelines recommend sputum culture to be performed monthly for the first 3 months after completing initial treatment and every 2 months thereafter for 1 year. A recent study has evaluated the role of anti- P. aeruginosa IgG antibodies. Key results from this study demonstrated that a positive Pa-IgG antibody test had high sensitivity (95%) and moderate specificity (74%) in patients with chronic P. aeruginosa infection. In patients with new P. aeruginosa isolation, eradication therapy was administered to all patients. Notably, eradication (negative sputum) at 12 months was more commonly (89.5%) seen in patients with a negative antibody test than in patients with a positive test (15.8%), suggesting that the baseline analysis of Pa-IgG antibodies may be useful in determining the likely efficacy of eradication therapy.

LONG-TERM TREATMENTS OF BRONCHIECTASIS

Should long-term or rotational antibiotics be used?

Bacterial infection (any) is associated with more frequent and more severe exacerbations. However, the effects are greater with P. aeruginosa infection with increased mortality (OR: 2–2.9), hospital admissions (OR: 2–6.6), exacerbations (one per year), worse lung function and poorer HRQoL (St George’s Respiratory Questionnaire (SGRQ): 18.2 points lower). Direct correlations between bacterial load and inflammation have been demonstrated in adults and children. Inflammatory products, such as neutrophil elastase, have also been independently associated with exacerbation frequency and lung function decline. Thus, reducing both bacterial colonization and interlinked inflammation could independently affect the course of disease.

A Cochrane review of antibiotic therapy in patients with bronchiectasis included 18 trials (1157 persons, 13% children). Antibiotics administered for 4–83 weeks (inhaled or oral) against ‘short term as needed’ or placebo showed a significant reduction in pulmonary exacerbations (271 per 1000 in intervention compared with 546 per 1000 in controls). There was also a reduction in hospitalizations (37 per 1000 in intervention compared with 87 per 1000 in controls). No significant changes in FEV, (reported in 88% of studies) were shown but reductions in sputum purulence and volume, systemic inflammatory markers and SGRQ were described in the studies when these were measured.

Bronchiectasis guidelines recommend long-term antibiotics for those with ≥3 exacerbations per year, with or
without chronic infection with *P. aeruginosa*, but the more recent guideline suggests use for ≥2 exacerbations in the community or one hospitalization as indications for long-term antibiotics. None of the guidelines have recommended rotational antibiotic use, although this practice is standard care in CF with inhaled antibiotics.

However, long-term antibiotic use has important disadvantages in particular on antimicrobial resistance as described in the Cochrane review (155 per 1000 in intervention compared with 50 per 1000 in controls). The development of resistance is an inevitable consequence of taking long-term antibiotics. The evolution of resistance is also influenced by treatment adherence (better adherence—less resistance documented). The current benefit-risk of improving the future course of disease versus emerging antimicrobial resistance has given rise to four recent Cochrane systematic reviews to assess the antibiotic effects in patients with bronchiectasis.

What is the role of nebulized antibiotics and which is the most useful?

The place of nebulized antibiotics is well established in CF. To date, none have been approved or registered for the treatment of patients with bronchiectasis. A number of randomized placebo-controlled trials investigating tobramycin, gentamicin, colistin, aztreonam and ciprofloxacin have been undertaken (Table 2). The majority involved older adults (mean age of these studies ranges from 57 to 69 years) who had chronic *P. aeruginosa* infection and advanced pulmonary disease. The studies varied in duration from 2 weeks (on/off for 12 cycles) or 1 month (on/off for one to six cycles) or 6 months to 12 months continuous. While there have been some clinical and/or microbiological improvement, the results compared to similar trials in CF populations have generally been less positive and inconsistent. The longer courses (6–12 months) of colistin or gentamicin showed significant reductions in exacerbations (33–49% with treatment vs 59–80% with placebo) and increased time to first exacerbation (median days to exacerbation of 120 and 165 with treatment compared with 61 and 111 with placebo). A similar finding was reported in one of the four ciprofloxacin studies. Only one study using 6 months of nebulised tobramycin (TOBI; Novartis Pharmaceuticals Corporation, East Hanover, New Jersey) reported reduction in hospitalizations (by 74%) but interestingly no difference in the success rate of treatment arms showed an increase in respiratory exacerbations, and a 30% reduction in hospitalization rates (Table 3). In addition, there was a 50% reduction in antibiotic use (all) and a significant improvement in weight-for-age (+1.3 compared with +0.2 Z-score).

Azithromycin, in comparison with other macrolides, is notable for its high intracellular accumulation and its ability to prevent biofilm formation by impairing quorum sensing signals. It also has a lower burden of treatment as daily, three times a week or even weekly dosing is possible. Macrolides are generally well tolerated but a major concern is evolution of antimicrobial resistance. While resistance was similar in the groups at baseline, treatment arms showed an increase (88% had resistant strain(s)) compared with placebo (26%; all isolates). In one study, erythromycin resistance of *Streptococci* isolates was 27.7% (active) compared with 0.04% (placebo) after 12 months of therapy. Similarly, after 20 months of azithromycin, there was significantly lower carriage of *H. influenzae* and *M. catarrhalis* but seven times greater risk of azithromycin-resistant bacterial carriage.

Adherence to antibiotics impacted rates of resistance. In patients taking ≥70% of medication, there were

There have been no published trials evaluating inhaled antibiotics in children. While *P. aeruginosa* infection is rare at this age, such treatment may be more efficacious given the greater potential of earlier disease stage (less structural changes), possibility of lung growth and this population may be more similar in age to those in the CF studies.

An increase in adverse events with treatment has repeatedly been described, occurring more often than in CF trials—notably bronchoconstriction and wheeze often necessitating termination of treatment. Surprisingly, such events appear less frequently with the dry powder devices. The emergence of resistant microorganisms with a fourfold increase in minimal inhibitory concentration for *P. aeruginosa* occurs in 7–50% of the treated groups.

Three bronchiectasis guidelines recommend that patients having more than three exacerbations annually and or those chronically infected with *P. aeruginosa* could be considered for inhaled antibiotics with no preferred protocol given.

Who should receive macrolides, and which one, for how long?

Three RCT including 341 adults examining azithromycin (in two) and erythromycin (in one) for 6–12 months consistently showed a reduction in exacerbation frequency (34–66%), a doubling of median time to next exacerbation, yet a variable effect in lung function (improvement in FEV1 of 3–4% in two studies) and QoL questionnaires (improvement in one). In children, an RCT of weekly azithromycin for a mean duration of 20 months in 89 participants demonstrated a 50% reduction in respiratory exacerbations, and a 30% reduction in hospitalization rates. In addition, there was a 50% reduction in antibiotic use (all) and a significant improvement in weight-for-age (+1.3 compared with +0.2 Z-score). Azithromycin, in comparison with other macrolides, is notable for its high intracellular accumulation and its ability to prevent biofilm formation by impairing quorum sensing signals. It also has a lower burden of treatment as daily, three times a week or even weekly dosing is possible. Macrolides are generally well tolerated but a major concern is evolution of antimicrobial resistance. While resistance was similar in the groups at baseline, treatment arms showed an increase (88% had resistant strain(s)) compared with placebo (26%; all isolates). In one study, erythromycin resistance of *Streptococci* isolates was 27.7% (active) compared with 0.04% (placebo) after 12 months of therapy. Similarly, after 20 months of azithromycin, there was significantly lower carriage of *H. influenzae* and *M. catarrhalis* but seven times greater risk of azithromycin-resistant bacterial carriage.

Adherence to antibiotics impacted rates of resistance. In patients taking ≥70% of medication, there were
lower rates of any pathogens identified and fewer macrolide-resistant organisms. After 6 months of study completion without azithromycin, the macrolide resistance for S. pneumoniae declined significantly from 79% to 7%, although resistance remained high for S. aureus. A further caution is the increased risk of macrolide therapy when prescribed for any indication to cause hearing loss, tinnitus and cardiac arrhythmias (ventricular arrhythmias, torsade de pointes and prolonged QT) and sudden cardiac death. This has largely been described in the elderly and those with severe disease, significant other co-morbidities and on other QT-prolonging medication.112,113 A further concern is the failure to recognize non-tuberculous mycobacterial infection (NTM) in the patient with bronchiectasis prior to or emerging during macrolide therapy. Monotherapy with macrolides may increase rates of macrolide-resistant NTM. Whilst one study suggested the emergence of Mycobacterium abscessus infection in adults with CF on long-term azithromycin therapy,114 this has not been confirmed in three other studies where azithromycin was associated with reduced risk of M. abscessus.115–117 Studies specifically in the bronchiectasis population are required to better understand the association, particularly as there is in vitro evidence that azithromycin can impair autophagic and phagosomal macrophage degradation.118 Recent bronchiectasis guidelines recommend screening sputum in patients with bronchiectasis with a minimum of one negative NTM culture prior to commencing macrolide therapy.119 In his recent review, Hill recommended sputum induction or even bronchoscopy sampling should be considered in the non-sputum productive patient.118

Guidelines recommend macrolides for those with frequent pulmonary exacerbations or chronic P. aeruginosa infection10,11,14,15 or for any chronic infection with a pathogen identified13 for 12–24 months with adherence being critical to reduce emerging antimicrobial resistance.

What is the role of airway clearance techniques (physiotherapy, mucolytics and exercise)?

This area of management will be the basis for another review within this series and will not be covered in depth here. In summary, guidelines currently recommend regular chest physiotherapy to be tailored to the individual and regular exercise. Trials of hypertonic saline or mannitol are recommended in adult patients with difficulty in expectorating sputum and poor QoL. Dornase alpha is not recommended.10,11,13–15

Are there any anti-inflammatory medications to consider in management?

There is an overlap of patients with asthma, COPD and bronchiectasis but with airway inflammation present in all and many having asthma-like symptoms, inhaled corticosteroids may be potentially useful in all. A recent Cochrane review included seven studies with 380 adults describing no significant differences from baseline in FEV1, average exacerbation frequency or QoL when used for 6 months or less.64 A single study similarly showed no significant difference in FEV1 or other clinical parameters after 12 months. One trial in 40 adults used high-dose inhaled budesonide for 3 months and then randomized to 3 months continued high-dose budesonide or medium-dose budesonide with a long-acting beta-agonist.119 The combination led to improved dyspnoea index (1.39 vs 0.1), increase in cough-free days (15.3% vs 3%) and a reduction in rescue beta-agonist inhalations required per week (−3.2 compared with −0.2) with no change in HRQoL, FEV1 or hospitalizations. Two other small studies; one using fluticasone and salmeterol showed lung function improvement; the other using combined inhaled corticosteroid and short-acting beta-agonist reported reduced sputum and fewer days of hospitalization.120

A number of small trials have looked at the effect of other anti-inflammatory medication in bronchiectasis achieving some reduction in inflammatory markers but without translation into significant clinical improvements. Two early studies using inhaled121 or oral indomethacin122 for 2–4 weeks involving less than 10 patients reported reduced sputum volume, improved the Borg Dyspnoea Scale score123 and significantly reduced neutrophil chemotaxis and degradation products with no change in bacterial density.124 Azithromycin (modulates inflammation by an unknown mechanism) reduced neutrophil activation and inflammatory markers with improvements in SGRQ when used in a cross-over study for 3 months in 32 adults chronically infected with P. aeruginosa.125 A cysteine-X-cysteine chemokine receptor-2 antagonist ‘AZD5069’ (to block IL8 binding and neutrophil migration) used for 4 weeks in 52 adults reduced sputum neutrophils by 69% but inflammatory markers increased and no clinical benefits were demonstrated.126 A neutrophil elastase inhibitor ‘AZD9668’ used for 4 weeks in 38 adults did not change sputum neutrophil numbers but did decrease sputum inflammatory markers.124

There has also been in vitro exploration of novel non-antibiotic macrolides with similar anti-inflammatory effects as azithromycin but negligible antibiotic activity.126 These improved human alveolar macrophage activity to phagocytose non-typeable H. influenzae and apoptotic epithelial cells with a reduction in inflammatory markers. This could be especially important for children with early disease and chronic infection with H. influenzae.

While these avenues warrant exploration, caution is advised. A double-blind RCT of a leukotriene B4 receptor antagonist in 420 individuals with CF planned for 24 weeks was stopped after an interim analysis showed increased exacerbations and more serious adverse events in the treated group.128 The compound was subsequently shown to decrease airway neutrophils but increase P. aeruginosa numbers in CF mice.127 Such concerns were further emphasized in a study of infliximab, used for 24 weeks in 234 patients with COPD which had no effects on designated outcomes but a trend to increased pneumonia in the treated group.128 Similarly, two trials of inhaled corticosteroid in COPD reported increased pneumonia and a 16-fold increase in non-tuberculous mycobacterium infection.103,129

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CONCLUSIONS, FUTURE DIRECTIONS AND CHALLENGES

This review has emphasized that more evidence to support clinical decision-making is required, specific for patients with bronchiectasis. Despite a growth in the numbers of study reports, including new and repurposed antibiotics, mucolytic therapies and physical therapies, not all recent studies have supported the implementation of the specific therapy into the clinic. Encouragingly, the event of Bronchiectasis Registries provides an enhanced understanding of the prevalence and natural history of bronchiectasis. Several therapeutic approaches have shown significant promise. Some examples of these approaches include the international multicentre consortium funded by the European Union (Inhaled Antibiotics in Bronchiectasis and Cystic Fibrosis, www.iabcproject.com/, accessed 20 July 2018), studies of indigenous nations from Australia, New Zealand and North America4,5,47,130 and studies of lung clearance index as a clinical trial endpoint for patients with bronchiectasis.135,136

Several challenges remain:
1 How to deal with the heterogeneity of the bronchiectasis population in choosing clinical trial populations?
2 What are the best outcome measures in adults and children?
3 How to fund such trials, particularly investigator-initiated studies?
4 How to undertake studies in indigenous populations?
5 How to develop novel trial designs and validated trial endpoints for children with bronchiectasis?

Challenges for the clinician include:
1 How to decide on specific therapies?
2 How to implement proven therapies, particularly in the diverse population and specifically in the indigenous population?
3 How to study interventions and to support treatment adherence within the bronchiectasis population?
4 How to balance the advantage to the individual of prolonged antibiotics use versus the inevitable emergence of antimicrobial resistance both in the individual and in the community?

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The Authors

S.C.B. is Executive Director—Research and Executive Director—Heart and Lung, Metro North Hospital and Health Service and a Senior Physician, Thoracic Program, The Prince Charles Hospital in Brisbane. He leads the Lung Bacteria Laboratory at QIMR Berghofer Medical Research Institute and his research interests include the suppurative lung disease microbiology and acquisition pathways for human infection. J.S.E. is Professor of Respiratory Medicine at Imperial College and the Royal Brompton Hospital London and Professor of Respiratory Medicine at Queen’s University Belfast. He leads the Innovative Medicines Initiative Program ihaled Antibiotics in Bronchiectasis and Cystic fibrosis (iABC), re-purposing antibiotics for inhaled delivery in bronchiectasis and CF. His research interests are focused on innate immunity and infection in chronic lung disease. C.A.B. is a Paediatric Respiratory Specialist at Starship Children’s Health, Auckland, and an Associate Professor at the University of Auckland. Her research interests are long-term outcomes from early infection, especially in indigenous children, and the prevention of disease and disease progression in children with bronchiectasis or CF.

REFERENCES


Pulmonary exacerbations in bronchiectasis


98 Donovan T, Felix LM, Chalmers JD, Milan SJ, Mathioudakis AG, Spencer S. Continuous versus intermittent antibiotics for bronchiectasis. Cochrane Database of Systematic Reviews 2018; CD012733.


