Macrolide antibiotics for non-cystic fibrosis bronchiectasis

Kelly, Carol; Evans, David J.; Chalmers, James D.; Crossingham, Iain; Spencer, Sally; Relph, Nicola

Published in:
Cochrane Database of Systematic Reviews

DOI:
10.1002/14651858.CD012406

Publication date:
2016

Document Version
Publisher's PDF, also known as Version of record

Cochrane Library

Cochrane Database of Systematic Reviews

Macrolide antibiotics for non-cystic fibrosis bronchiectasis (Protocol)

Kelly C, Evans DJ, Chalmers JD, Crossingham I, Spencer S, Relph N, Felix LM, Milan SJ

Kelly C, Evans DJ, Chalmers JD, Crossingham I, Spencer S, Relph N, Felix LM, Milan SJ.
Macrolide antibiotics for non-cystic fibrosis bronchiectasis.
Cochrane Database of Systematic Reviews 2016, Issue 10. Art. No.: CD012406.
DOI: 10.1002/14651858.CD012406.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Protocol]

Macrolide antibiotics for non-cystic fibrosis bronchiectasis

Carol Kelly[1], David J Evans[2], James D Chalmers[3], Iain Crossingham[4], Sally Spencer[1], Nicola Relph[5], Lambert M Felix[1], Stephen J Milan[6]

[1]Faculty of Health and Social Care, Edge Hill University, Ormskirk, UK. [2]Thoracic Medicine, Hemel Hempstead Hospital, Hemel Hempstead, UK. [3]University of Dundee, Ninewells Hospital and Medical School, Dundee, UK. [4]East Lancashire Hospitals NHS Trust, Blackburn, UK. [5]Physical Activity and Sport, Edge Hill University, Ormskirk, UK. [6]Lancaster Health Hub, Lancaster University, Lancaster, UK

Contact address: Sally Spencer, Faculty of Health and Social Care, Edge Hill University, Ormskirk, UK. spencesa@edgehill.ac.uk.

Editorial group: Cochrane Airways Group.
Publication status and date: New, published in Issue 10, 2016.

Citation: Kelly C, Evans DJ, Chalmers JD, Crossingham I, Spencer S, Relph N, Felix LM, Milan SJ. Macrolide antibiotics for non-cystic fibrosis bronchiectasis. *Cochrane Database of Systematic Reviews* 2016, Issue 10. Art. No.: CD012406. DOI: 10.1002/14651858.CD012406.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To determine the impact of macrolide antibiotics in the treatment of adults and children with non-cystic fibrosis bronchiectasis.

BACKGROUND

Description of the condition

Bronchiectasis is a chronic respiratory disease characterised by abnormal and irreversible dilatation and distortion of the smaller airways (Pasteur 2010). Bacterial colonisation of the damaged airways leads to chronic cough and sputum production, often with breathlessness and with further structural damage to the airways. Diagnosis is by computed tomography (CT) scanning of the chest when the appropriate clinical symptoms are identified (Chang 2010) but asymptomatic radiological evidence of bronchiectasis is possible (Kwak 2010).

Bronchiectasis has many causes, generally involving either major or repeated insults to the lungs. Severe infections including pneumonia, tuberculosis and pertussis may cause bronchiectasis, particularly if they occur during childhood whilst lungs are still developing. Connective tissue disorders and defects in the immune system are other common causes of bronchiectasis, but many cases are idiopathic. Cystic fibrosis leads to a severe, progressive bronchiectasis and is usually considered a separate entity from 'non-cystic fibrosis' bronchiectasis. This review will exclude bronchiectasis secondary to cystic fibrosis.

Estimates of the prevalence of bronchiectasis vary considerably. Although it has previously been considered a relatively rare disease (Kolbe 1996), more recent studies have suggested an increasing prevalence, particularly in those over 75 years (Weycker 2005), and higher prevalence rates in low-income and middle-income countries (Habesoglu 2011). Prevalence rates per 100,000 were estimated at 0.5 in Finland and 3.7 in New Zealand though these data are more than 10 years old (European Lung White Book 2013). Higher prevalence rates are associated with the over 60s, women, and vary by ethnicity (Chang 2003; Seitz 2012). Recent data suggest that incidence and prevalence in the UK may be higher than previously estimated (Quint 2016). Over a nine-year period to 2013, point prevalence rates per 100,000 rose from 350.5 to

566.1 in women and from 301.2 to 485.5 in men. This reflects an increase of more than 60% with approximately 263,000 adults living with bronchiectasis in 2013. Similarly, the incidence rates per 100,000 person-years rose from 21.2 to 35.2 in women and from 18.2 to 26.9 in men, a 63% increase in new cases to over 15,000 in 2013. However, these increases may be due to improved diagnosis resulting from easier access to high quality CT scanners, rather than a true rise in prevalence (Goeminne 2016).

Mortality rates in England and Wales rose by 3% per year between 2001 to 2007 (Roberts 2010), and hospitalisations also increased by 3% per year over a nine-year period in the US (Seitz 2010). Average mortality rates per 100,000 general population in Europe are estimated at 0.3 in 27 of the 28 countries in the EU (ranging from 0.01 in Germany to 1.18 in the UK) and 0.2 in nine non-EU countries (ranging from 0.01 in Azerbaijan to 0.67 in Kyrgyzstan), based on 2005 to 2009 data (European Lung White Book 2013). The recent UK study reported higher age-adjusted mortality rates, with estimates 2.26 times higher in women and 2.14 times higher in men compared to the general population (Quint 2016).

Description of the intervention

Chronic airway infection with pathogens such as *Pseudomonas aeruginosa* and *Haemophilus influenzae* and neutrophil-mediated airway inflammation are the key drivers of disease progression and poor outcome in bronchiectasis (Chalmers 2012; Chalmers 2014; Finch 2015). Long-term antibiotic therapy is therefore often prescribed with the intention of suppressing bacterial load and reducing airway inflammation (Chalmers 2012). This in turn aims to reduce exacerbations, improve symptoms and improve quality of life (Haworth 2014). Prolonged antibiotic treatment can be administered in the form of oral or inhaled antibiotics. Inhaled antibiotics have the advantage of delivering a higher dose of the drug directly to the site of bronchiectasis infection, with less potential for collateral damage and resistance, however, they are often time consuming to administer (Brodt 2014). Oral antibiotics by contrast are typically cheaper and easier to administer than inhaled antibiotics.

Oral antibiotics may be given at lower dose than those used to treat acute infections, with the aim to reduce adverse effects and promote compliance (Haworth 2014). Macrolide antibiotics are antibacterial agents with anti-inflammatory and immunomodulatory properties (Haworth 2014). Long-acting macrolide antibiotics such as azithromycin can be given intermittently rather than requiring daily dosing. Penicillins, tetracyclines and macrolides have all been tested as prolonged therapy in bronchiectasis (Pasteur 2010). National guidelines for bronchiectasis, such as those from the British Thoracic Society suggest considering the use of long-term antibiotic treatment in patients with three or more exacerbations per year (Pasteur 2010).

Long-term use of macrolides in bronchiectasis is supported by their ease of administration, their effectiveness in cystic fibrosis and other neutrophilic lung diseases and their reported anti-inflammatory properties (Saiman 2003). Balanced against this is the potential for macrolides to induce antibiotic resistance, the potential for antibiotic-related adverse effects, hearing impairment and cardiotoxicity (Serisier 2013).

How the intervention might work

Exacerbations, symptoms and quality of life are directly linked to bacterial infection and airway inflammation in bronchiectasis (Chalmers 2012; Chalmers 2014). Macrolides are given as both antibacterial and anti-inflammatory drugs, although it is unclear which of these properties is primarily responsible for the clinical effect observed in cystic fibrosis or bronchiectasis. Macrolides bind reversibly to the 50s ribosomal subunit, preventing bacterial protein synthesis (Haworth 2014). They therefore have broad activity against Gram-positive organisms such as *Staphylococci* and *Streptococci*, and a degree of activity against Gram-negative organisms such as *Haemophili.* Interestingly, they show no bacteriocidal activity against *P aeruginosa* but may modify virulence by interfering with quorum sensing and virulence factors (Kohler 2010).

The anti-inflammatory effects of macrolides have been known for decades, classically demonstrated in their effectiveness against diffuse panbronchiolitis (Amsden 2005). Macrolides contain a macrocytic lactone ring that is thought to be responsible for the majority of the anti-inflammatory effects (Haworth 2014). Macrolides are classified according to the number of lactone rings as 14-, 15- and 16-member ring macrolides. Macrolides have potentially beneficial effects at every level of the 'vicious cycle' of bronchiectasis. They reduce the secretion of pro-inflammatory cytokines from epithelial cells, inhibit leukocyte recruitment to the airway, inhibit neutrophil activation and reduce oxidative stress (Zarogoulidis 2012).

Thus potential benefits of macrolides will include the suppression of bacterial infection, leading to reduced exacerbations, reduced cough and sputum production and improved lung function and quality of life.

Why it is important to do this review

Non-cystic fibrosis bronchiectasis is associated with a mortality rate more than twice that of the general population; 2.26 times higher in women and 2.14 times higher in men (Quint 2016). Frequent exacerbations impair quality of life and lead to progressive lung damage with permanent loss of lung function (Martínez-García 2007). Drug interventions which are effective in reducing the frequency of exacerbations should therefore be of both short- and long-term benefit to patients with bronchiectasis. A Cochrane review of short-term antibiotics showed there was little evidence on which to base a recommendation, with one small trial showing evidence of global improvement and pathogen eradica-

tion in sputum (Wurzel 2011). A further Cochrane review of long-term antibiotic therapy included 18 trials of moderate quality and provided evidence of a reduction in exacerbation frequency and hospitalisation, but an increase in drug resistance (Hnin 2015). Neither of these reviews examined effects by class of antibiotics and did not specifically subgroup by macrolide therapy. A Cochrane overview concluded that further evidence is required on the efficacy of antibiotics in terms of eradication of specific bacterial colonisation and the extent of antibiotic resistance (Welsh 2015). The importance of this question was further reinforced by recent recommendations from the European Task Force on bronchiectasis that named research on macrolide therapy as one of the key priorities in bronchiectasis (Aliberti 2016). Macrolides may potentially reduce bronchiectasis exacerbations. Given their drawbacks, particularly cardiac toxicity (Ray 2012) and the potential for selecting for antibiotic-resistant organisms (Leclercq 2002), robust evidence for their effectiveness is needed for them to be used with confidence for this indication.

This review is being conducted alongside two other closely related reviews: 'Dual antibiotics for non-cystic fibrosis bronchiectasis' and 'Head to head trials of antibiotics for non-cystic fibrosis bronchiectasis.'

OBJECTIVES

To determine the impact of macrolide antibiotics in the treatment of adults and children with non-cystic fibrosis bronchiectasis.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) of at least four weeks duration. We will include cross-over studies, but will only use data from the first pre-cross-over phase to eliminate potentially irreversible carry-over effects (e.g. antibiotic resistance). We will include studies reported as full-text, those published as abstract only, and unpublished data.

Types of participants

We will include adult and paediatric participants diagnosed with bronchiectasis by bronchography, plain film chest radiograph, or high-resolution computed tomography who report daily sputum expectoration for at least three months. We will not exclude participants diagnosed by radiography alone. When a study includes participants with different respiratory conditions, we will only include that study if there is a separate subgroup analysis conducted for participants with bronchiectasis. Studies will be excluded if participants have been receiving continuous or high-dose antibiotics immediately before the study, or if they have received a diagnosis of cystic fibrosis, sarcoidosis or allergic bronchopulmonary aspergillosis. We will define the paediatric population as those from six months to 18 years of age.

Types of interventions

We will include studies comparing macrolide antibiotics with placebo, standard care or non-macrolide antibiotics in the long-term management of stable bronchiectasis. These different comparisons will be considered separately. We will exclude studies looking at short-term macrolides for the treatment (as opposed to prevention) of exacerbations of bronchiectasis.

Types of outcome measures

Where possible we will assess exacerbation and hospitalisation rates at 12 months. We will estimate annual rates in studies reporting shorter follow-up times. We will collect outcome data at a range of follow-up points that will best reflect the available evidence from included studies, e.g. end of study, end of follow-up, change from baseline.

Primary outcomes

1. Exacerbations (defined using study authors' criteria).
2. Hospitalisation (defined using study authors' criteria).
3. Adverse events and serious adverse events using the definitions from Hansen 2015 as follows.

i) Adverse events are unwanted outcomes undetectable by the patient; usually identified by laboratory tests (e.g. biochemical, haematological, immunological, radiological, pathological tests) or by clinical investigations (e.g. gastrointestinal endoscopy, cardiac catheterisation).

ii) Serious adverse events are those that result in death or life-threatening events; requirement for hospitalisation or prolongation of existing hospitalisation; persistent or significant disability; or congenital anomalies, or are events that are considered medically important.

Secondary outcomes

1. Sputum volume and purulence.
2. Measures of lung function (e.g. forced expiratory volume in one second (FEV_1)).
3. Systemic markers of infection (e.g. leucocyte count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR)).
4. Adverse events (e.g. cardiac arrhythmias, gastrointestinal symptoms, hearing impairment).

5. Mortality (we will extract and report whether this is defined as all-cause or bronchiectasis-related in the individual studies).

6. Emergence of resistance to antibiotics.

7. Exercise capacity (e.g. the Six-Minute Walk Distance test (6MWD)).

8. Quality of life (e.g. St George Respiratory Questionnaire (SGRQ)).

Reporting one or more of the outcomes listed here in the study will not be an inclusion criterion for the review.

Search methods for identification of studies

Electronic searches

We will identify studies from the Cochrane Airways Group's Specialised Register (CAGR), which is maintained by the Information Specialist for the Group. The Register contains trial reports identified through systematic searches of bibliographic databases including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), AMED (Allied and Complementary Medicine), and PsycINFO, and handsearching of respiratory journals and meeting abstracts (please see Appendix 1 for further details). We will search all records in the CAGR using the search strategy in Appendix 2.

We will also conduct a search of the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch).

We will search all databases from their inception to the present, and we will impose no restriction on language of publication.

Searching other resources

We will check reference lists of all primary studies and review articles for additional references. We will search relevant manufacturers' websites for study information.

We will search for errata or retractions from included studies published in full-text on PubMed (www.ncbi.nlm.nih.gov/pubmed) and report the date this was done within the review.

Data collection and analysis

Selection of studies

Two review authors (James Chalmers (JC) and David Evans (DE) will independently screen titles and abstracts for inclusion of all the potential studies we identify as a result of the search and code them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We will retrieve the full-text study reports/publication and two review authors (JC and DE) will independently screen the full-text, identify studies for inclusion, and identify and record reasons for exclusion of the ineligible studies. We will resolve any disagreement through discussion or, if required, we will consult a third review author (Sally Spencer (SS) or Stephen J Milan (SJM). We will identify and exclude duplicates and collate multiple reports of the same study so that each study rather than each report is the unit of interest in the review. We will record the selection process in sufficient detail so as to complete a PRISMA flow diagram and Characteristics of excluded studies table (Moher 2009).

Data extraction and management

We will use a data collection form for study characteristics and outcome data which has been piloted on at least one study in the review. One review author (Lambert Felix (LF) will extract study characteristics from included studies. We will extract the following study characteristics.

1. Methods: study design, total duration of study, details of any 'run in' period, number of study centres and location, study setting, withdrawals, and date of study.

2. Participants: number, mean age, age range, gender, severity of condition, diagnostic criteria, baseline lung function, smoking history, inclusion and exclusion criteria.

3. Interventions: intervention, comparison, concomitant medications, and excluded medications.

4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.

5. Notes: funding for study, and notable conflicts of interest of study authors.

Two review authors (LF and Carol Kelly (CK) will independently extract outcome data from the included studies. We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. We will resolve disagreements by consensus or by involving a third review author (SS or SJM). One review author (LF) will transfer data into the Review Manager (RevMan 2014) file. We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (CK) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Two review authors (Nicola Relph (NR) and LF) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will resolve any disagreements by discussion or by involving another review author (SS or SJM). We will assess the risk of bias according to the following domains.

1. Random sequence generation.

2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will grade each potential source of bias as high, low or unclear and provide a quote from the study report together with a justification for our judgement in the 'Risk of bias' table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will consider blinding separately for different key outcomes where necessary (e.g. for unblinded outcome assessment, risk of bias for all-cause mortality may be very different than for a patient-reported pain scale). Where information on risk of bias relates to unpublished data or correspondence with a study author, we will note this in the 'Risk of bias' table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome.

Assessment of bias in conducting the systematic review

We will conduct the review according to this published protocol and report any deviations form it in the 'Differences between protocol and review' section of the systematic review.

Measures of treatment effect

We will analyse dichotomous data as odds ratios and continuous data as mean difference or standardised mean difference. We will analyse hospitalisation and exacerbation rates as rate ratios where possible. We will enter data presented as a scale with a consistent direction of effect.

We will undertake meta-analyses only where this is meaningful i.e. if the treatments, participants and the underlying clinical question are similar enough for pooling to make sense.

We will narratively describe skewed data reported as medians and interquartile ranges.

Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If two comparisons (e.g. drug A versus placebo and drug B versus placebo) are combined in the same meta-analysis, we will halve the control group to avoid double-counting.

Unit of analysis issues

In all included studies the unit of analysis will be the participant. In terms of exacerbation rates and admission rates we plan to focus on the number of events experienced by the participant during the trial. Where cross-over trials are included we will only use data from the first pre-cross-over phase to minimise potential bias from carry-over effects.

Dealing with missing data

We will contact investigators or study sponsors in order to verify key study characteristics and obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only). Where this is not possible, and the missing data are thought to introduce serious bias, we will explore the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Assessment of heterogeneity

We will use the I^2 statistic to measure heterogeneity among the studies in each analysis. If we identify substantial heterogeneity we will report it and explore possible causes by prespecified subgroup analysis.

Assessment of reporting biases

If we are able to pool more than 10 studies, we will create and examine a funnel plot to explore possible small study and publication biases.

Data synthesis

Outcomes will be included in meta-analyses where the study designs, interventions and outcomes are similar. Where substantial heterogeneity (> 50%) is identified we will report outcomes in the text, giving direction and size of the effect along with the strength of the evidence (risk of bias). It is likely that antibiotic studies will vary by population, design and outcomes, therefore meta-analysis using a random-effects model would be most appropriate. However, where there are few studies or the effects of interventions across studies are not randomly distributed (for example, with publication bias), the estimates from a random-effects model may be unreliable or biased. It is likely that this review will only include a small number of low powered studies, therefore we will use a fixed-effect model, reported with 95% confidence intervals (CI), and evaluate the impact of model choice using a sensitivity analysis. We will synthesise and report dichotomous and continuous data separately for each outcome (e.g. exacerbation/no exacerbation or exacerbation duration). Where end-of-study point estimates and change from baseline scores are reported we will analyse these separately.

'Summary of findings' table

We will create a 'Summary of findings' table using the following primary and secondary outcomes: exacerbations, hospitalisation, serious adverse events, deaths, quality of life. We will use the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of a body of evidence as it relates to the studies which contribute

data to the meta-analyses for the prespecified outcomes. We will use methods and recommendations described in Section 8.5 and Chapter 12 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) using GRADEproGDT software (GRADEproGDT). We will justify all decisions to downgrade or upgrade the quality of studies using footnotes and we will make comments to aid the reader's understanding of the review where necessary.

Subgroup analysis and investigation of heterogeneity

We plan to carry out the following subgroup analyses.

1. Children versus adults.
2. Macrolides versus other classes of long-term antibiotics.
3. Type of macrolide.
4. Dose and frequency.
5. Duration.

We will use the following outcomes in subgroup analyses.

1. Exacerbations.
2. Hospitalisation.
3. Serious adverse events.

We will use the formal test for subgroup interactions in Review Manager (RevMan 2014).

Sensitivity analysis

We plan to evaluate the effects of methodological study quality by removing those at high or unclear risk of bias for the domains of random sequence generation or allocation concealment.
We will also conduct a separate analysis including only those comparing macrolides with a placebo-controlled group.

ACKNOWLEDGEMENTS

We would like to thank Edge Hill University for their support for this review. We would also like to thank Cochrane Airways for their support.

Rebecca Normansell was the Editor and commented critically on the protocol.

The Background and Methods sections of this protocol are based on a standard template used by Cochrane Airways.

REFERENCES

Additional references

Aliberti 2016
Aliberti S, Masefield S, Polverino E, De Soyza A, Loebinger MR, Menendez R, et al. Research priorities in bronchiectasis: a consensus statement from the EMBARC Clinical Research Collaboration. *European Respiratory Journal* 2016;**48**(3):632–47.

Amsden 2005
Amsden GW. Anti-inflammatory effects of macrolides--an under appreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions?. *Journal of Antimicrobial Chemotherapy* 2005;**55**(1):10–21.

Brodt 2014
Brodt AM, Stovold E, Zhang L. Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review. *European Respiratory Journal* 2014;**44**(2):382–93.

Chalmers 2012
Chalmers JD, Smith MP, McHugh BJ, Doherty C, Govan JR, Hill AT. Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 2012;**186**(7):657–65.

Chalmers 2014
Chalmers JD, Goeminne P, Aliberti S, Melissa J, McDonnell MJ, Lonni S, et al. The Bronchiectasis Severity Index: an international derivation and validation study. *American Journal of Respiratory and Critical Care Medicine* 2014;**189**(5):576–85. [DOI: 10.1164/rccm.201309-1575OC]

Chang 2003
Chang AB, Masel JP, Boyce NC, Wheaton G, Torzillo PJ. Non-CF bronchiectasis: clinical and HRCT evaluation. *Pediatric Pulmonology* 2003;**35**(6):477–83.

Chang 2010
Chang AB, Bell SC, Byrnes CA, Grimwood K, Holmes P, King PT, et al. Chronic suppurative lung disease and bronchiectasis in children and adults in Australia and New Zealand: A position statement from the Thoracic Society of Australia and New Zealand and the Australian Lung Foundation. *Medical Journal of Australia* 2010;**193**(6):356–65.

European Lung White Book 2013
Gibson GJ, Loddenkemper R, Sibille Y, Lundbäck B, editor(s). European Lung White Book: Respiratory Health and Disease in Europe. European Respiratory Society, 2013. Available from www.erswhitebook.org/.

Finch 2015
Finch S, McDonnell MJ, Abo-Leyah H, Aliberti S, Chalmers JD. A comprehensive analysis of the impact of Pseudomonas aeruginosa colonization on prognosis in adult bronchiectasis. *Annals of the American Thoracic Society* 2015;**12**(11):1602–11.

Goeminne 2016
Goeminne PC, De Soyza A. Bronchiectasis: how to be an orphan with many parents?. *European Respiratory Journal* 2016;**47**(1):10–3.

GRADEproGDT [Computer program]
GRADE Working Group, McMaster University. GRADEproGDT. Version accessed 14 July 2016. Hamilton (ON): GRADE Working Group, McMaster University, 2014.

Habesoglu 2011
Habesoglu MA, Ugurlu AO, Eyuboglu FO. Clinical, radiologic, and functional evaluation of 304 patients with bronchiectasis. *Annals of Thoracic Medicine* 2011;**6**(3): 131–6.

Hansen 2015
Hansen MP, Thorning S, Aronson JK, Beller EM, Glasziou PP, Hoffmann TC, et al. Adverse events in patients taking macrolide antibiotics versus placebo for any indication. *Cochrane Database of Systematic Reviews* 2015, Issue 8. [DOI: 10.1002/14651858.CD011825]

Haworth 2014
Haworth CS, Bilton D, Elborn JS. Long term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. *Respiratory Medicine* 2014;**108**(1): 1397–408.

Higgins 2011
Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Hnin 2015
Hnin K, Nguyen C, Carson KV, Evans DJ, Greenstone M, Smith BJ. Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. *Cochrane Database of Systematic Reviews* 2015, Issue 8. [DOI: 10.1002/14651858.CD001392.pub3]

Kohler 2010
Kohler T, Perron GG, Buckling A, van Delden C. Quorum sensing inhibition selects for virulence and co-operation in pseudomonas aeruginosa. *PLoS Pathogens* 2010;**6**(5): e1000883.

Kolbe 1996
Kolbe J, Wells AU. Bronchiectasis: a neglected cause of respiratory morbidity and mortality. *Respirology (Carlton, Vic.)* 1996;**1**(4):221–5. [PUBMED: 9441110]

Kwak 2010
Kwak HJ, Moon JY, Choi YW, Kim TH, Sohn JW, Yoon HJ, et al. High prevalence of bronchiectasis in adults: analysis of CT findings in a health screening program. *Tohoku Journal of Experimental Medicine* 2010;**222**(4): 237–42.

Leclercq 2002
Leclercq R. Mechanisms of resistance to macrolides and lincosamides: Nature of the resistance elements and their clinical implications. *Clinical Infectious Diseases* 2002;**34** (4):482–92.

Lefebvre 2011
Lefebvre C, Manheimer E, Glanville J. Chapter 6: Searching for studies. In: Higgins JP, Green S, editor(s). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration, 2011. Available from handbook.cochrane.org.

Martínez-García 2007
Martínez-García MA, Soler-Cataluña JJ, Perpiñá-Tordera M, Román-Sánchez P, Soriano J. Factors associated with lung function decline in adult patients with stable non-cystic fibrosis bronchiectasis. *Chest* 2007;**132**(5):1565–72.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman D. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Medicine* 2009;**6**(7): e1000097. [DOI: 10.1371/journal.pmed.1000097]

Pasteur 2010
Pasteur MC, Bilton D, Hill AT, British Thoracic Society Bronchiectasis (non-CF) Guideline Group. British Thoracic Society Guidelines for non-CF bronchiectasis. *Thorax* 2010;**65 Suppl 1**:i1–58.

Quint 2016
Quint JK, Millett ERC, Joshi M, Navaratnam V, Thomas SL, Hurst JR, et al. Changes in the incidence, prevalence and mortality of bronchiectasis in the UK from 2004 to 2013: a population-based cohort study. *European Respiratory Journal* 2016;**47**(1):186–93. [DOI: 10.1183/13993003.01033-2015]

Ray 2012
Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM. Azithromycin and the risk of cardiovascular death. *New England Journal of Medicine* 2012;**366**:1881–90.

RevMan 2014 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014.

Roberts 2010
Roberts HJ, Hubbard R. Trends in bronchiectasis mortality in England and Wales. *Respiratory Medicine* 2010;**104**: 981–5.

Saiman 2003
Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, et al. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA* 2003;**290** (13):1749–56.

Seitz 2010
Seitz AE, Olivier KN, Steiner CA, Montes de Oca R, Holland SM, Prevots DR. Trends and burden of bronchiectasis-associated hospitalizations in the United States. *Chest* 2010;**138**:944–9.

Seitz 2012
Seitz AE, Olivier KN, Adjemian J, Holland SM, Prevots DR. Trends in bronchiectasis among Medicare beneficiaries in the United States, 2000-2007. *Chest* 2012;**142**(2):432–9.

Serisier 2013
Serisier DJ. Risk of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respiratory Medicine* 2013;**1**(3): 262–74.

Welsh 2015
Welsh EJ, Evans DJ, Fowler SJ, Spencer S. Interventions for bronchiectasis: an overview of Cochrane systematic reviews. *Cochrane Database of Systematic Reviews* 2015, Issue 7. [DOI: 10.1002/14651858.CD010337.pub2]

Weycker 2005
Weycker D, Edelsberg J, Oster G, Tino G. Prevalence and economic burden of bronchiectasis. *Clinical Pulmonary Medicine* 2005;**12**(4):205–9.

Wurzel 2011
Wurzel D, Marchant JM, Yerkovich ST, Upham JW, Masters IB, Chang AB. Short courses of antibiotics for children and adults with bronchiectasis. *Cochrane Database of Systematic Reviews* 2011, Issue 6. [DOI: 10.1002/14651858.CD008695.pub2]

Zarogoulidis 2012
Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K. Macrolides from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases. *European Journal of Clinical Pharmacology* 2012;**68**(5):479–503.

* *Indicates the major publication for the study*

APPENDICES

Appendix 1. Sources and search methods for the Cochrane Airways Group's Specialised Register (CAGR)

Electronic searches: core databases

Database	Frequency of search
CENTRAL (the Cochrane Library)	Monthly
MEDLINE (Ovid)	Weekly
Embase (Ovid)	Weekly
PsycINFO (Ovid)	Monthly
CINAHL (EBSCO)	Monthly
AMED (EBSCO)	Monthly

Handsearches: core respiratory conference abstracts

Conference	Years searched
American Academy of Allergy, Asthma and Immunology (AAAAI)	2001 onwards
American Thoracic Society (ATS)	2001 onwards
Asia Pacific Society of Respirology (APSR)	2004 onwards
British Thoracic Society Winter Meeting (BTS)	2000 onwards
Chest Meeting	2003 onwards
European Respiratory Society (ERS)	1992, 1994, 2000 onwards
International Primary Care Respiratory Group Congress (IPCRG)	2002 onwards
Thoracic Society of Australia and New Zealand (TSANZ)	1999 onwards

MEDLINE search strategy used to identify trials for the CAGR

Bronchiectasis search

1. exp Bronchiectasis/
2. bronchiect$.mp.
3. bronchoect$.mp.
4. kartagener$.mp.
5. (ciliary adj3 dyskinesia).mp.
6. (bronchial$ adj3 dilat$).mp.
7. or/1-6

Filter to identify randomised controlled trials (RCTs)

1. exp "clinical trial [publication type]"/
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. Animals/
10. Humans/
11. 9 not (9 and 10)
12. 8 not 11

The MEDLINE strategy and RCT filter (Lefebvre 2011) are adapted to identify trials in other electronic databases.

Appendix 2. Search strategy to identify relevant trials from the CAGR

#1 BRONCH:MISC1
#2 MeSH DESCRIPTOR Bronchiectasis Explode All
#3 bronchiect*
#4 #1 or #2 or #3
#5 MeSH DESCRIPTOR Macrolides Explode 1 2 3
#6 macrolide*
#7 azithromycin*
#8 clarithromycin*
#9 erythromycin*
#10 roxithromycin*
#11 spiramycin*
#12 telithromycin*
#13 troleandomycin*
#14 Josamycin*
#15 Midecamycin*
#16 Oleandomycin*
#17 Solithromycin*
#18 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17
#19 #4 AND #18
(Note: in search line #1, MISC1 denotes the field in the record where the reference has been coded for condition, in this case, bronchiectasis)

CONTRIBUTIONS OF AUTHORS

All authors contributed to the Background section.

Stephen J Milan and Sally Spencer contributed to the Methods section.

DECLARATIONS OF INTEREST

Sally Spencer, Carol Kelly and Nicola Relph are named co-investigators on a study funded by Edge Hill University to develop a series of reviews on bronchiectasis and Lambert Felix is supported by that funding. No funding was received for this systematic review by any of the other authors.

James D Chalmers declares grant support from Pfizer, AstraZeneca and GlaxoSmithKline. In addition he is part of an innovative medicines initiative consortium that includes Novartis and Basilea. He has participated in advisory boards for Bayer HealthCare, Chiesi and Raptor Pharmaceuticals. He has received fees for speaking from Napp, AstraZeneca, BI and Pfizer. None of these conflicts of interest are related to the work of this review and are unrelated to the topic of the review.

SOURCES OF SUPPORT

Internal sources

- Edge Hill University, UK.

Funded Lambert Felix to provide support for a series of reviews on bronchiectasis.

External sources

- National Institute for Health Research (NIHR), UK.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Airways. The views and opinions expressed therein are those of the review authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS, or the Department of Health.