

Bronchiectasis (non-cystic fibrosis), acute exacerbation: antimicrobial prescribing

Evidence review

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1 Context

1.1 Background

Bronchiectasis is a chronic respiratory condition characterised by abnormal, dilated, thick-walled bronchi. This guideline focuses on acute exacerbations of non-cystic fibrosis bronchiectasis, which is bronchiectasis not related to underlying cystic fibrosis, but more commonly caused by a previous severe lower respiratory tract infection.

Bronchiectasis typically presents with a chronic productive cough (or chronic wet cough in children) and symptoms can vary from intermittent expectoration and infection, to persistent daily expectoration of large volumes of purulent sputum. Complications of bronchiectasis include acute exacerbations, chronic bacterial colonisation, and haemoptysis which can be life-threatening ([NICE clinical knowledge summary – bronchiectasis](#)). It is estimated that 5 in every 1000 adults in the UK have bronchiectasis. The prognosis for people living with bronchiectasis varies widely but the prognosis is worse for people who have frequent exacerbations which can result in daily symptoms, progressive loss of lung function and a reduced life expectancy (NICE clinical knowledge summary – bronchiectasis).

An acute exacerbation of bronchiectasis is characterised by an acute deterioration of normal symptoms and signs usually over several days. It presents with worsening local symptoms (such as cough, increased sputum volume, change of sputum viscosity, or increased sputum purulence) with or without increased wheeze, breathlessness or haemoptysis. Fever or pleurisy may also be present. Depending on the severity of symptoms, and whether a person is systemically unwell, an acute exacerbation of bronchiectasis can be managed in primary care or may require hospital admission (NICE clinical knowledge summary – bronchiectasis, [British Thoracic Society guideline for non-CF bronchiectasis 2010](#)).

Acute exacerbations of bronchiectasis can be caused by a spectrum of bacteria including: *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis* and *Pseudomonas aeruginosa*. In a study where 437 sputum samples of people with non-cystic fibrosis bronchiectasis were cultured for microbiology, 1 or more pathogen was found on 339 (78%) occasions ([Altenburg 2013](#)). The most frequently cultured organisms were: *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Moraxella catarrhalis* and *Haemophilus parainfluenzae*, with these organisms accounting for 87% of the total number of pathogens.

An acute exacerbation of bronchiectasis requires antimicrobial treatment. However, evidence assessing the efficacy and safety of antibiotics specifically for the treatment of an acute exacerbation of bronchiectasis (or the optimal dose, duration and route

of administration) is limited. The bacteria responsible for acute exacerbations of bronchiectasis can be different to those responsible for exacerbations of other respiratory conditions, such as COPD. Therefore, antibiotic choice is often guided by previous sputum cultures where available.

In many people with bronchiectasis, the airways are chronically infected with a number of pathogens and antibiotic prophylaxis to prevent an exacerbation, as well as antibiotic treatment of an exacerbation, may be considered.

This guideline covers the treatment and antimicrobial prevention of acute exacerbations of non-cystic fibrosis bronchiectasis.

1.2 *Managing infections that require antibiotics*

An acute exacerbation of bronchiectasis is a bacterial infection needing treatment with an antibiotic. However, antibiotics should only be started when there is clear evidence of infection. In some instances the condition of the patient may necessitate prompt effective antibiotic treatment within 1 hour of diagnosis (or as soon as possible) in patients who have [sepsis](#) or life threatening infection, in these patients therapy should not be delayed but sputum and/or blood samples for culture should, if possible, be obtained prior to treatment.

In line with the Department of Health and Social Care guidance ([Start Smart Then Focus](#)) and the NICE guideline on [antimicrobial stewardship](#) consider reviewing intravenous antibiotic prescriptions at 48 to 72 hours, documenting response to treatment and any available microbiology results to determine if the antibiotic should be continued or switched to a narrower spectrum or an oral antibiotic.

1.2.1 Antibiotic prescribing strategies

The NICE guideline on [antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#) provides recommendations for prescribers on prescribing antimicrobials. The recommendations guide prescribers in decisions about antimicrobial prescribing and include recommending that they follow local and national guidelines, use the shortest effective course length and record their decisions, particularly when these decisions are not in line with guidelines. The recommendations also advise that prescribers take into account the benefits and harms for a person when prescribing an antimicrobial, such as possible interactions, co-morbidities, drug allergies and the risks of healthcare associated infections.

The NICE guideline on antimicrobial stewardship: changing risk-related behaviours in the general population recommends that resources and advice should be available for people who are prescribed antimicrobials to ensure they are taken as instructed at the correct dose, via the correct route, for the time specified. Verbal advice and written information that people can take away about how to use antimicrobials

correctly should be given, including not sharing prescription-only antimicrobials with anyone other than the person they were prescribed or supplied for, not keeping them for use another time and returning unused antimicrobials to the pharmacy for safe disposal and not flushing them down toilets or sinks.

1.3 Safety information

1.3.1 Safety netting

The NICE guideline on [antimicrobial stewardship: changing risk-related behaviours in the general population](#) recommends that safety netting advice should be shared with everyone who has an infection (regardless of whether or not they are prescribed or supplied with antimicrobials).

This should include:

- how long symptoms are likely to last with and without antimicrobials
- what to do if symptoms get worse
- what to do if they experience adverse effects from the treatment
- when they should ask again for medical advice.

1.3.2 Medicines safety

Antibiotic-associated diarrhoea is estimated to occur in 2 to 25% of people taking antibiotics, depending on the antibiotic used ([NICE clinical knowledge summary: diarrhoea – antibiotic associated](#)).

About 10% of the general population claim to have a penicillin allergy; this has often been because of a skin rash that occurred during a course of penicillin in childhood. Fewer than 10% of people who think they are allergic to penicillin are truly allergic. See the NICE guideline on [drug allergy: diagnosis and management](#) for more information. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics ([BNF October 2018](#)).

Fluoroquinolones, including ciprofloxacin, cause arthropathy in the weight-bearing joints of immature animals and are generally not recommended in children or young people who are growing. Tendon damage (including rupture) has been reported rarely in people receiving fluoroquinolones ([BNF October 2018](#)), and the European Medicines Agency's Pharmacovigilance Risk Assessment Committee ([press release October 2018](#)) has recommended restricting the use of these antibiotics following a review of disabling and potentially long-lasting side effects mainly involving muscles, tendons and bones and the nervous system. This includes a recommendation to not use fluoroquinolones for mild or moderately severe infections unless other antibiotics cannot be used.

Tetracyclines, including doxycycline, can deposit in growing bone and teeth (by binding to calcium) causing staining and occasionally dental hypoplasia. They should not be given to children under 12 years, or to pregnant or breast-feeding women. The absorption of tetracyclines is reduced by antacids, milk, and aluminium, calcium, iron, magnesium and zinc salts. Common side effects include nausea, vomiting, diarrhoea, dysphagia, and oesophageal irritation ([BNF October 2018](#)).

Macrolides, including azithromycin, clarithromycin and erythromycin, are an alternative to penicillins in people with penicillin allergy. They should be used with caution in people with a predisposition to QT interval prolongation. Nausea, vomiting, abdominal discomfort, and diarrhoea are the most common side effects of macrolides. These are less frequent with clarithromycin than with erythromycin ([BNF October 2018](#)).

Inhaled antibiotics, such as colistimethate sodium, can cause bronchospasm; lung function should be measured before and after the initial dose and the person monitored for bronchospasm ([BNF October 2018](#)).

1.4 Antimicrobial resistance

The consumption of antimicrobials is a major driver for the development of antibiotic resistance in bacteria, and the 3 major goals of antimicrobial stewardship are to:

- optimise therapy for individual patients
- prevent overuse, misuse and abuse, and
- minimise development of resistance at patient and community levels.

The NICE guideline on [antimicrobial stewardship: systems and processes for effective antimicrobial medicine use](#) recommends that the risk of antimicrobial resistance for individual patients and the population as a whole should be taken into account when deciding whether or not to prescribe an antimicrobial.

When antimicrobials are necessary to treat an infection that is not life-threatening, a narrow-spectrum antibiotic should generally be first choice. Indiscriminate use of broad-spectrum antibiotics creates a selective advantage for bacteria resistant even to these 'last-line' broad-spectrum agents, and also kills normal commensal flora leaving people susceptible to antibiotic-resistant harmful bacteria such as *C. difficile*. For infections that are not life-threatening, broad-spectrum antibiotics (for example, co-amoxiclav, fluoroquinolones and cephalosporins) need to be reserved for second-choice treatment when narrow-spectrum antibiotics are ineffective ([CMO report 2011](#)).

With prolonged antibiotic use for prophylaxis, for example in the prevention of acute exacerbations of bronchiectasis, the emergence of resistance is a particular concern.

The systematic review by Hnin et al. 2015 discusses resistance to macrolide antibiotics in particular (following azithromycin use) and supports the importance of patient selection to reduce the risk of widespread emergence of antimicrobial resistance.

The [ESPAUR report 2017](#) reported that antibiotic prescribing reduced by 5% between 2012 and 2016, with declines across the majority of antibiotic groups. However, significant regional variation in antibiotic use continues to occur. The number of prescriptions dispensed in the GP setting decreased by 13% between 2012 and 2016, largely driven by reductions in use of penicillins. Secondary care, despite some progress observed in 2015, has not had a sustained reduction in total antibiotic prescribing. However, from 2015 to 2016 hospitals reduced their use of the ultra-broad spectrum antibiotics piperacillin/tazobactam and carbapenems.

1.5 Other considerations

1.5.1 Medicines adherence

Medicines adherence may be a problem for some people with medicines that require frequent dosing (for example, some antibiotics; NICE guideline on [medicines adherence](#)). Longer treatment durations, for example with prophylactic antibiotics, may also cause problems with medicines adherence for some people.

1.5.2 Regulatory status

Inhaled antibiotics, such as such as colistimethate sodium, are not licensed for use in non-cystic fibrosis bronchiectasis, so use for this indication would be off label.

2 Evidence

The evidence identified in this guideline is for non-antimicrobial and antimicrobial interventions for treating acute exacerbations of non-cystic fibrosis bronchiectasis, and antimicrobial interventions for preventing acute exacerbations of bronchiectasis. Physical therapies, such as airway clearance techniques, were out of scope of this guideline, as were non-antimicrobial interventions for preventing acute exacerbations.

This evidence review originally also considered non-antimicrobial interventions for preventing acute exacerbations of acute bronchiectasis. However, following stakeholder consultation, the scope was amended to remove the section on non-antimicrobial interventions for preventing acute exacerbations of bronchiectasis.

2.1 *Treatment of acute exacerbations of bronchiectasis*

2.1.1 Non-antimicrobial interventions

No systematic reviews or RCTs were found that investigated non-antimicrobial interventions, such as mucoactive agents, bronchodilators or inhaled corticosteroids, for the treatment of acute exacerbations of bronchiectasis.

2.1.2 Antimicrobial interventions

The only evidence identified for antimicrobial interventions for the treatment of acute exacerbations of bronchiectasis was 1 RCT of oral antibiotics plus nebulised antibiotics compared with oral antibiotics plus placebo in adults ([Bilton et al. 2016](#)). There was no evidence in children or young people, and no randomised placebo-controlled trials of antibiotics were identified.

2.1.2.1 *Oral antibiotics plus nebulised antibiotics*

GRADE profile - Oral ciprofloxacin plus nebulised tobramycin versus oral ciprofloxacin plus placebo in adults with an acute exacerbation of bronchiectasis

Summary

The evidence review for oral ciprofloxacin plus nebulised tobramycin is based on 1 double-blind, placebo-controlled RCT (n=53) in adults with an acute exacerbation of bronchiectasis. At the time of exacerbation, participants were randomised to 750 mg oral ciprofloxacin plus 300 mg nebulised tobramycin twice daily or 750 mg oral ciprofloxacin plus nebulised placebo twice daily for 14 days. Participants were only

included if they had a history of chronic *Pseudomonas aeruginosa* infection and if the *Pseudomonas aeruginosa* showed sensitivity to ciprofloxacin at the time of enrollment. An acute exacerbation was defined as the presence of an increase in at least 2 of the following symptoms: cough, sputum volume, sputum purulence, dyspnoea, or wheezing; and at least 1 of the following symptoms: fever, malaise, increased white blood cell count, increased C-reactive protein; and laboratory evidence of purulent sputum.

There was no significant difference in resolution of exacerbation at both 21 and 42 days with ciprofloxacin plus tobramycin compared with ciprofloxacin plus placebo. Exacerbations were resolved in 50.0% of participants in the ciprofloxacin plus tobramycin group compared with 70.4% in the ciprofloxacin plus placebo group (RR 0.71; 95% CI 0.45 to 1.12) at 21 days (low quality evidence), and 34.6% compared with 44.4% (RR 0.78; 95% 0.40 to 1.53) at 42 days (very low quality evidence).

There was no significant difference in adverse events overall, but participants in the ciprofloxacin plus tobramycin group experienced a significant increase in wheeze compared with the ciprofloxacin plus placebo group (RR 3.38; 95% CI 1.26 to 9.02; moderate quality evidence).

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Oral ciprofloxacin plus placebo	Oral ciprofloxacin plus nebulised tobramycin		
Resolution of exacerbation Day 21	Relative risk 0.71 (CI 95% 0.45 - 1.12) Based on data from 53 patients in 1 study	704 per 1000	500 per 1000	Low Due to serious inconsistency, Due to serious imprecision ¹	We are uncertain whether oral ciprofloxacin plus nebulised tobramycin increases or decreases resolution of exacerbation at day 21
Importance: Critical		Difference: 204 fewer per 1000 (CI 95% 387 fewer - 84 more)			
Resolution of exacerbation Day 42	Relative risk 0.78 (CI 95% 0.40 - 1.53) Based on data from 53 patients in 1 study	444 per 1000	346 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ²	We are uncertain whether oral ciprofloxacin plus nebulised tobramycin increases or decreases resolution of exacerbation at day 42
Importance: Critical		Difference: 98 fewer per 1000 (CI 95% 266 fewer - 235 more)			
	Relative risk 1.88	200 per 1000	376 per 1000	Very Low	We are uncertain

Eradication of <i>Pseudomonas aeruginosa</i>	(CI 95% 0.73 - 4.79) Based on data from 49 patients in 1 study	Difference: 176 more per 1000 (CI 95% 54 fewer - 758 more)		Due to serious inconsistency, Due to very serious imprecision ³	whether oral ciprofloxacin plus nebulised tobramycin increases or decreases eradication of <i>Pseudomonas aeruginosa</i>
Importance: Critical					
Adverse events	Relative risk 0.88 (CI 95% 0.73 - 1.05) Based on data from 53 patients in 1 study	963 per 1000	847 per 1000	Low Due to serious inconsistency, Due to serious imprecision ⁴	Oral ciprofloxacin plus nebulised tobramycin may have little or no effect on adverse events
Importance: Critical		Difference: 116 fewer per 1000 (CI 95% 260 fewer - 48 more)			
Adverse event - wheeze	Relative risk 3.38 (CI 95% 1.26 - 9.02) Based on data from 53 patients in 1 study	148 per 1000	500 per 1000	Moderate Due to serious inconsistency ⁵	Oral ciprofloxacin plus nebulised tobramycin probably increases wheeze
Importance: Critical		Difference: 352 more per 1000 (CI 95% 38 more - 1187 more)			
<p>¹ Risk of bias: No serious. Inconsistency: Serious. N/A; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral ciprofloxacin plus nebulised tobramycin; Publication bias: No serious.</p> <p>² Risk of bias: No serious. Inconsistency: Serious. N/A; Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm with oral ciprofloxacin plus nebulised tobramycin; Publication bias: No serious.</p> <p>³ Risk of bias: No serious. Inconsistency: Serious. N/A; Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm with oral ciprofloxacin plus nebulised tobramycin; Publication bias: No serious.</p> <p>⁴ Risk of bias: No serious. Inconsistency: Serious. N/A; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference with oral ciprofloxacin plus nebulised tobramycin; Publication bias: No serious.</p> <p>⁵ Risk of bias: No serious. Inconsistency: Serious. N/A; Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.</p>					

References

Bilton Diana, Henig Noreen, Morrissey Brian, and Gotfried Mark (2006) Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest* 130(5), 1503-10

2.2 Prevention of acute exacerbations of bronchiectasis

2.2.1 Antimicrobial interventions

2.2.1.1 All antibiotics

GRADE profile - All antibiotics versus placebo or standard care in adults, young people and children with stable state bronchiectasis

Summary

The evidence review for continuous prolonged antibiotics (4 or more weeks duration) in adults, young people and children is based on 1 systematic review ([Hnin et al. 2015](#)) of 18 RCTs (n=1157; mostly adults). Diagnosis of bronchiectasis was confirmed by chest radiograph, bronchography or high-resolution computed tomography (HRCT) and participants were included if they reported daily sputum for at least 3 months.

The systematic review and meta-analysis pooled outcomes for oral and nebulised antibiotics, and outcomes for adults, young people and children. These overall results are reported in this section. Subgroup analyses for oral antibiotics, oral macrolide antibiotics, and nebulised antibiotics, in adults and children, have been reported separately where possible below.

Overall, antibiotics significantly decreased the number of participants with exacerbations (37.7% compared with 54.6%; RR 0.71, 95% CI 0.54 to 0.93; low quality evidence), hospitalisations, and the exacerbation rate compared with placebo. However they also significantly increased the emergence of resistance (RR 2.79, 95% CI 1.08 to 7.23; moderate quality evidence) and diarrhoea (RR 2.89, 95% CI 1.24 to 7.72; low quality evidence) compared with placebo.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo or standard care	Antibiotics		
Number of participants with exacerbations Importance: Critical	Relative risk 0.71 (CI 95% 0.54 - 0.93) Based on data from 654 patients in 10 studies	546 per 1000	388 per 1000	Low Due to serious inconsistency, Due to serious imprecision ¹	Antibiotics may decrease number of participants with exacerbations
		Difference: 158 fewer per 1000 (CI 95% 251 fewer - 38 fewer)			
Hospitalisations Importance: Critical	Relative risk 0.44 (CI 95% 0.21 - 0.94) Based on data from 643 patients in 7 studies	87 per 1000	38 per 1000	Moderate Due to serious imprecision ²	Antibiotics probably decrease hospitalisations
		Difference: 49 fewer per 1000 (CI 95% 69 fewer - 5 fewer)			

Withdrawals due to intolerable side effects Importance: Critical	Relative risk 0.90 (CI 95% 0.62 - 1.32) Based on data from 683 patients in 10 studies	132 per 1000 Difference: 13 fewer per 1000 (CI 95% 50 fewer - 42 more)	119 per 1000	Low Due to very serious imprecision ³	Antibiotics may have little or no difference on withdrawals due to intolerable side effects
Adverse event - diarrhoea Importance: Critical	Relative risk 2.89 (CI 95% 1.24 - 6.72) Based on data from 231 patients in 3 studies	63 per 1000 Difference: 119 more per 1000 (CI 95% 15 more - 360 more)	182 per 1000	Low Due to serious risk of bias, Due to serious imprecision ⁴	Antibiotics may increase diarrhoea
Adverse event - rash Importance: Critical	Relative risk 1.78 (CI 95% 0.67 - 4.75) Based on data from 140 patients in 3 studies	72 per 1000 Difference: 56 more per 1000 (CI 95% 24 fewer - 270 more)	128 per 1000	Very Low Due to serious risk of bias, Due to very serious imprecision ⁵	We are uncertain whether antibiotics increases or has no effect on rash
Adverse event - wheeze Importance: Critical	Relative risk 13.00 (CI 95% 0.76 - 222.75) Based on data from 74 patients in 1 study	13 per 1000 Difference: 156 more per 1000 (CI 95% 3 fewer - 2883 more)	169 per 1000	Low Due to serious inconsistency, Due to serious imprecision ⁶	Antibiotics may have little or no effect on wheeze
Adverse event - chest pain or palpitations Importance: Critical	Relative risk 3.66 (CI 95% 0.21 - 63.46) Based on data from 274 patients in 3 studies	7 per 1000 Difference: 19 more per 1000 (CI 95% 6 fewer - 437 more)	26 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ⁷	We are uncertain whether antibiotics increase or have no effect on chest pain or palpitations
Adverse event - increased cough Importance: Critical	Relative risk 0.54 (CI 95% 0.03 - 10.52) Based on data from 198 patients in 2 studies	139 per 1000 Difference: 64 fewer per 1000 (CI 95% 135 fewer - 1323 more)	75 per 1000	Very Low Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision ⁸	We are uncertain whether antibiotics increase or have no effect on increased cough
Adverse event - nausea Importance: Critical	Relative risk 0.96 (CI 95% 0.38 - 2.47) Based on data from 275 patients in 4 studies	102 per 1000 Difference: 4 fewer per 1000 (CI 95% 63 fewer - 150 more)	98 per 1000	Very Low Due to serious risk of bias, Due to very serious imprecision ⁹	We are uncertain whether antibiotics increase or decrease nausea
Adverse event - hemoptysis Importance: Critical	Relative risk 0.91 (CI 95% 0.66 - 1.25) Based on data from 310 patients in 3 studies	197 per 1000 Difference: 18 fewer per 1000 (CI 95% 67 fewer - 49 more)	179 per 1000	Very Low Due to serious risk of bias, Due to very serious imprecision ¹⁰	We are uncertain whether antibiotics increase or have no effect on hemoptysis
Adverse event - bronchospasm	Odds ratio 2.24 (CI 95% 0.74 - 6.83)	52 per 1000	109 per 1000	Very Low	We are uncertain whether antibiotics

Importance: Critical	Based on data from 189 patients in 2 studies	Difference: 57 more per 1000 (CI 95% 13 fewer - 221 more)		Due to serious risk of bias, Due to very serious imprecision ¹¹	increase or have no effect on bronchospasm
Deaths Importance: Critical	Relative risk 1.22 (CI 95% 0.25 - 5.98) Based on data from 595 patients in 7 studies	7 per 1000	9 per 1000	Very Low Due to serious risk of bias, Due to very serious imprecision ¹²	There were too few deaths, to determine whether antibiotics made a difference
Emergence of resistance Importance: Critical	Relative risk 2.79 (CI 95% 1.08 - 7.23) Based on data from 431 patients in 6 studies	47 per 1000	146 per 1000	Moderate Due to serious imprecision ¹³	Antibiotics probably increase emergence of resistance
Exacerbation rates Importance: Critical	Based on data from 230 patients in 3 studies	Difference: SMD 0.8 lower (CI 95% 1.32 lower - 0.29 lower)		Low Due to serious inconsistency, Due to serious imprecision ¹⁴	Antibiotics may decrease exacerbation rates

¹ **Risk of bias: No serious. Inconsistency: Serious.** Heterogeneity >50% (I² calculated by NICE as 68% using a random effects model); **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no appreciable benefit with antibiotics; **Publication bias: No serious.**

² **Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no appreciable benefit with antibiotics; **Publication bias: No serious.**

³ **Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with antibiotics; **Publication bias: No serious.**

⁴ **Risk of bias: Serious.** Random sequence generation and allocation concealment methods not reported for 2/3 studies.; **Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no appreciable harm with antibiotics; **Publication bias: No serious.**

⁵ **Risk of bias: Serious.** Random sequence generation and allocation concealment methods not reported for 2/3 studies.; **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with antibiotics; **Publication bias: No serious.**

⁶ **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT.; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with antibiotics; **Publication bias: No serious.**

⁷ **Risk of bias: No serious. Inconsistency: Serious.** Heterogeneity >50% (I² calculated by NICE as 52% using a random effects model).; **Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with antibiotics; **Publication bias: No serious.**

⁸ **Risk of bias: Serious.** Incomplete outcome reporting; **Inconsistency: Serious.** Heterogeneity >50% (I² calculated by NICE as 76% using a random effects model); **Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with antibiotics.; **Publication bias: No serious.**

⁹ **Risk of bias: Serious.** Inadequate randomisation and allocation concealment method reporting.; **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with antibiotics; **Publication bias: No serious.**

¹⁰ **Risk of bias: Serious.** Inadequate random sequence generation and allocation concealment method reporting; **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with antibiotics; **Publication bias: No serious.**

¹¹ **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with antibiotics; **Publication bias: No serious.**

¹² **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** Non-significant effect, 95% CI of RR crosses null. ; **Publication bias: No serious.**

¹³ **Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no appreciable harm with antibiotics; **Publication bias: No serious.**

¹⁴ **Risk of bias: No serious. Inconsistency: Serious.** Heterogeneity >50% (I² calculated by NICE as 68% using a random effects model); **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 0.5 STD, data are consistent with no appreciable benefit with antibiotics ; **Publication bias: No serious.**

References

Hnin Khin, Nguyen Chau, Carson Kristin V, Evans David J, Greenstone Michael, and Smith Brian J (2015) Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. The Cochrane database of systematic reviews (8), CD001392

2.2.1.2 Oral antibiotics (subgroup analysis)

GRADE profile - Oral antibiotics versus placebo or standard care in adults with stable state bronchiectasis

Summary

The evidence review for continuous oral antibiotics in adults with stable state bronchiectasis is based on a sub-group analysis of 8 RCTs from 1 systematic review ([Hnin et al. 2015](#)). The antibiotics used were azithromycin (3 studies), roxithromycin (1 study), erythromycin (2 studies), amoxicillin (1 study), and penicillin or oxytetracycline (1 study). The duration of intervention ranged from 8 to 52 weeks.

All RCTs were placebo-controlled, with the exception of 2 in which usual care was used as the comparator. All RCTs were double-blind with the exception of 1 which was open-label and 1 which did not report the blinding method.

Continuous oral antibiotics significantly reduced the exacerbation rate compared with placebo. However, there was no significant difference in the number of participants experiencing an exacerbation (32% compared with 58%; RR 0.54, 95% CI 0.22 to 1.35; low quality evidence) or hospitalisations between groups.

A non-significant increase in the emergence of resistance was reported in 1 trial of azithromycin for 24 weeks, with emergence of resistance reported for 2/46 people in the azithromycin group compared with 0/45 people in the control group.

There was no significant difference in adverse events, apart from diarrhoea which was increased in the oral antibiotic group.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo or standard treatment	Oral antibiotics		
Number of participants with exacerbations	Relative risk 0.54 (CI 95% 0.22 - 1.35) Based on data from 246 patients in 4 studies	579 per 1000	313 per 1000	Low Due to very serious imprecision ¹	Oral antibiotics may have little or no effect on number of participants with exacerbations
		Difference: 266 fewer per 1000 (CI 95% 452 fewer - 203 more)			
Hospitalisations	Relative risk 0.37 (CI 95% 0.09 - 1.59) Based on data from 341 patients in 3 studies	36 per 1000	13 per 1000	Low Due to very serious imprecision ²	Oral antibiotics may have little or no effect on hospitalisations
		Difference: 23 fewer per 1000 (CI 95% 33 fewer - 21 more)			
Withdrawals due to intolerable side effects	Relative risk 1.30 (CI 95% 0.53 - 3.19) Based on data from 369 patients in 5 studies	43 per 1000	56 per 1000	Low Due to very serious imprecision ³	Oral antibiotics may have little or no effect on withdrawals due to intolerable side effects
		Difference: 13 more per 1000 (CI 95% 20 fewer - 94 more)			
Adverse event - diarrhoea	Relative risk 2.89 (CI 95% 1.24 - 6.72) Based on data from 231 patients in 3 studies	63 per 1000	182 per 1000	Moderate Due to serious imprecision ⁴	Oral antibiotics probably increase diarrhoea
		Difference: 119 more per 1000 (CI 95% 15 more - 360 more)			
Adverse event - rash	Relative risk 1.78 (CI 95% 0.67 - 4.75) Based on data from 140 patients in 3 studies	72 per 1000	128 per 1000	Low Due to very serious imprecision ⁵	Oral antibiotics may have little or no effect on rash
		Difference: 56 more per 1000 (CI 95% 24 fewer - 270 more)			
Adverse event - chest pain or palpitations	Relative risk 0.93 (CI 95% 0.06 - 14.38) Based on data from 200 patients in 2 studies	10 per 1000	9 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ⁶	We are uncertain whether oral antibiotics increase or decreases chest pain or palpitations
		Difference: 1 fewer per 1000 (CI 95% 9 fewer - 134 more)			
Adverse event - nausea	Relative risk 0.81 (CI 95% 0.38 - 1.71) Based on data from 236 patients in 3 studies	120 per 1000	97 per 1000	Low Due to very serious imprecision ⁷	Oral antibiotics may have little or no effect on nausea
		Difference: 23 fewer per 1000 (CI 95% 74 fewer - 85 more)			
Adverse event - hemoptysis		611 per 1000	538 per 1000	Very Low	We are uncertain whether oral

	Relative risk 0.88 (CI 95% 0.63 - 1.23) Based on data from 112 patients in 1 study	Difference: 73 fewer per 1000 (CI 95% 226 fewer - 141 more)		Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision ⁸	antibiotics increase or decrease hemoptysis
Deaths	Relative risk 0.95 (CI 95% 0.09 - 10.11) Based on data from 312 patients in 3 studies	7 per 1000	7 per 1000	Very Low Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision ⁹	There were too few deaths, to determine whether oral antibiotics made a difference
Emergence of resistance	Relative risk 4.89 (CI 95% 0.24 - 99.18) Based on data from 91 patients in 1 study	0 per 1000	0 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ¹⁰	We are uncertain whether oral antibiotics increases or decreases emergence of resistance
Exacerbation rates	Based on data from 230 patients in 3 studies	Difference: SMD 0.8 lower (CI 95% 1.32 lower - 0.29 lower)		Low Due to serious inconsistency, Due to serious imprecision ¹¹	Oral antibiotics may decrease exacerbation rates
<ol style="list-style-type: none"> Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. At a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm with oral antibiotics; Publication bias: No serious. Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral antibiotics; Publication bias: No serious. Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. At a minimal important difference of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm with oral antibiotics; Publication bias: No serious. Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no appreciable benefit with oral antibiotics; Publication bias: No serious. Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral antibiotics. ; Publication bias: No serious. Risk of bias: No serious. Inconsistency: Serious. Not applicable. ; Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral antibiotics.; Publication bias: No serious. Risk of bias: No serious. Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral antibiotics.; Publication bias: No serious. Risk of bias: Serious. Selective outcome reporting; Inconsistency: Serious. Not applicable - single RCT.; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral antibiotics.; Publication bias: No serious. Risk of bias: Serious. Selective outcome reporting; Inconsistency: Serious. Not applicable. ; Indirectness: No serious. Imprecision: Very serious. Non-significant effect, 95% CI of RR crosses null. ; Publication bias: No serious. Risk of bias: No serious. Inconsistency: Serious. Not applicable - single RCT.; Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral antibiotics. ; Publication bias: No serious. 					

11. **Risk of bias: No serious. Inconsistency: Serious.** Heterogeneity > 50% (calculated by NICE as 68% using a random effects model); **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 0.5 standard deviations, data are consistent with no appreciable benefit with oral antibiotics. ; **Publication bias: No serious.**

References

Hnin Khin, Nguyen Chau, Carson Kristin V, Evans David J, Greenstone Michael, and Smith Brian J (2015) Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. The Cochrane database of systematic reviews (8), CD001392

GRADE profile - Oral antibiotics versus placebo in children and young people with stable state bronchiectasis

Summary

The evidence review for continuous oral antibiotics in children and young people (<14 years) with stable state bronchiectasis is based on 3 RCTs from 1 systematic review ([Hnin et al. 2015](#)). The trials investigated continuous oral antibiotics (roxithromycin, clarithromycin or azithromycin) for 12 weeks, 3 months, and 1 to 2 years respectively. Two trials were placebo-controlled and 1 compared oral antibiotics to supportive therapy (mucolytics, expectorants, and postural drainage). The findings from these studies may not be generalisable to the UK population; roxithromycin is not available in the UK and 1 trial was conducted in indigenous children in Australia and New Zealand where there is known to be a higher incidence of bronchiectasis.

In the 2 placebo-controlled trials that reported number of exacerbations as an outcome, there was no significant difference between oral antibiotics and placebo in the number of children or young people experiencing an exacerbation or hospitalisation.

Emergence of resistance was increased in the oral antibiotic group (RR 3.45, 95% CI 1.28 to 9.29; low quality evidence) . One RCT with azithromycin reported that the most common adverse events were non-pulmonary infections, which occurred in 71/112 events in the azithromycin group compared with 132/209 events in the placebo group. No evidence on other adverse events was available.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo	Oral antibiotics		
		750 per 1000	623 per 1000	Very Low	We are uncertain whether oral

Number of participants with an exacerbation Importance: Critical	Relative risk 0.83 (CI 95% 0.47 - 1.47) Based on data from 114 patients in 2 studies	Difference: 127 fewer per 1000 (CI 95% 397 fewer - 353 more)		Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision ¹	antibiotics increase or decrease exacerbations
Hospitalisations Importance: Critical	Relative risk 0.33 (CI 95% 0.09 - 1.12) Based on data from 89 patients in 1 study	205 per 1000	68 per 1000	Very Low Due to serious indirectness, Due to serious inconsistency, Due to serious imprecision ²	Oral antibiotics may have little or no effect on hospitalisations
		Difference: 137 fewer per 1000 (CI 95% 187 fewer - 25 more)			
Emergence of resistance Importance: Critical	Relative risk 3.45 (CI 95% 1.28 - 9.29) Based on data from 88 patients in 1 study	108 per 1000	373 per 1000	Low Due to serious indirectness, Due to serious inconsistency ³	Oral antibiotics may increase emergence of resistance
		Difference: 265 more per 1000 (CI 95% 30 more - 895 more)			
Deaths Importance: Critical	Relative risk (CI 95% -) Based on data from 78 patients in 1 study Follow up: 2 years.	0 per 1000	0 per 1000	Low Due to serious inconsistency, Due to serious imprecision ⁴	There were too few deaths, to determine whether continuous oral antibiotics made a difference
		(CI 95%)			
<p>1. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; Inconsistency: No serious. Indirectness: Serious. Differences between the intervention/comparator of interest and those studied; Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral antibiotics. ; Publication bias: No serious.</p> <p>2. Risk of bias: No serious. Inconsistency: Serious. Not applicable - single RCT.; Indirectness: Serious. Differences between the population of interest and those studied; Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with oral macrolides; Publication bias: No serious.</p> <p>3. Risk of bias: No serious. Inconsistency: Serious. Not applicable - single RCT.; Indirectness: Serious. Differences between the population of interest and those studied; Imprecision: No serious. Publication bias: No serious.</p> <p>4. Risk of bias: No serious. Inconsistency: Serious. Not applicable - single RCT.; Indirectness: No serious. Imprecision: Serious. Not assessable. ; Publication bias: No serious.</p>					

References

Hnin Khin, Nguyen Chau, Carson Kristin V, Evans David J, Greenstone Michael, and Smith Brian J (2015) Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. The Cochrane database of systematic reviews (8), CD001392

2.2.1.3 Oral macrolides (subgroup analysis)

GRADE profile - Continuous oral macrolides versus placebo or standard care in adults with stable state bronchiectasis

Summary

The evidence review for continuous oral macrolides in adults with stable state bronchiectasis is based on 6 RCTs from 1 systematic review ([Hnin et al. 2015](#)). The macrolides used were: azithromycin (3 studies), roxithromycin (1 study) and erythromycin (2 studies). The duration of intervention ranged from 8 to 52 weeks. All RCTs were placebo-controlled, with the exception of 2 in which usual care was used as the comparator. All RCTs were double-blind with the exception of 1 which was open-label and 1 which did not report the blinding method.

Continuous oral macrolides significantly reduced the number of participants experiencing an exacerbation compared with placebo (21.7% compared with 50.0%; RR 0.46, 95% CI 0.31 to 0.67; low quality evidence) and reduced the exacerbation rate. However, there was no significant difference in hospitalisations between groups.

Three studies reported the number of participants experiencing exacerbations, 1 of which reported a significant reduction in exacerbations in the treatment group (weighting 95%). This trial was a moderately sized trial (n=141) of oral azithromycin 500 mg 3 days a week (Monday, Wednesday and Friday) for 6 months. In this trial an exacerbation was defined as an increase in, or new onset of, more than one of the following: sputum volume, sputum purulence, or dyspnoea that required treatment with antibiotics. The other 2 trials (weighting 5%) also showed a reduction in exacerbations with roxithromycin 150 mg daily and erythromycin 500 mg twice a day, but these were non-significant.

Three studies reported exacerbation rates and all showed a significant reduction with oral macrolides compared with placebo. Interventions included azithromycin 250 mg daily, azithromycin 250 mg 3 times a week and erythromycin ethysuccinate 400 mg twice a day.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo or standard care	Continuous oral macrolides		
Number of participants with exacerbations	Relative risk 0.46 (CI 95% 0.31 - 0.67) Based on data from 208 patients in 3 studies	500 per 1000	230 per 1000	Low Due to serious risk of bias, Due to serious indirectness ¹	Continuous oral macrolides may decrease the number of
		Difference: 270 fewer per 1000 (CI 95% 345 fewer - 165 fewer)			

Importance: Critical					participants with exacerbations
Hospitalisations	Relative risk 0.37 (CI 95% 0.09 - 1.59) Based on data from 341 patients in 3 studies	36 per 1000	13 per 1000	Low Due to very serious imprecision ²	There were too few hospitalisations, to determine whether continuous oral macrolides made a difference
Importance: Critical		Difference: 23 fewer per 1000 (CI 95% 33 fewer - 21 more)			
Emergence of resistance	Relative risk 4.89 (CI 95% 0.24 - 99.18) Based on data from 91 patients in 1 study	0 per 1000	0 per 1000	Low Due to very serious imprecision ³	There were too few who experienced the emergence of resistance, to determine whether continuous oral macrolides made a difference
Importance: Critical		Difference: 0 fewer per 1000 (CI 95% 0 fewer - 0 fewer)			
Deaths	Relative risk (CI 95% -) Based on data from 200 patients in 2 studies	0 per 1000	0 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ⁴	There were too few deaths, to determine whether continuous oral macrolides made a difference
Importance: Critical		Difference: 0 fewer per 1000 (CI 95% 0 fewer - 0 fewer)			
Withdrawals (intolerable side effects)	Relative risk 1.09 (CI 95% 0.39 - 3.05) Based on data from 221 patients in 3 studies	56 per 1000	61 per 1000	Very Low Due to serious risk of bias, Due to very serious imprecision ⁵	We are uncertain whether continuous oral macrolides increase or have no effect on withdrawals due to intolerable side effects
Importance: Critical		Difference: 5 more per 1000 (CI 95% 34 fewer - 115 more)			
Adverse event – diarrhoea	Relative risk 8.37 (CI 95% 1.11 - 63.15) Based on data from 83 patients in 1 study	25 per 1000	209 per 1000	Moderate Due to very serious imprecision, Due to serious imprecision ⁶	Continuous oral macrolides probably increases diarrhoea slightly
Importance: Critical		Difference: 184 more per 1000 (CI 95% 3 more - 1554 more)			
Adverse event – nausea	Relative risk 0.59 (CI 95% 0.11 - 3.03) Based on data from 200 patients in 2 studies	92 per 1000	54 per 1000	Low Due to very serious imprecision ⁷	Continuous oral macrolides may have little or no effect on nausea
Importance: Critical		Difference: 38 fewer per 1000 (CI 95% 82 fewer - 187 more)			
Adverse event – rash	Relative risk 1.67 (CI 95% 0.59 - 4.68) Based on data from 104 patients in 2 studies	100 per 1000	167 per 1000	Low Due to very serious imprecision ⁸	We are uncertain whether continuous oral macrolides increase or decrease rash
Importance: Critical		Difference: 67 more per 1000 (CI 95% 41 fewer - 368 more)			
Exacerbation rates – continuous	Based on data from 230 patients in 3 studies	Difference: SMD 0.8 lower (CI 95% 1.32 lower - 0.29 lower)		Very Low Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision ⁹	We are uncertain whether continuous oral macrolides increase or decrease exacerbation rates
Importance: Critical					

1. **Risk of bias: Serious.** Inadequate randomisation method reporting; **Inconsistency: No serious.** **Indirectness: Serious.** Differences between the comparator of interest and those studied in Liu et al; **Imprecision: No serious.** **Publication bias: No serious.**
2. **Risk of bias: No serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with continuous oral macrolides; **Publication bias: No serious.**
3. **Risk of bias: No serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with continuous oral macrolides; **Publication bias: No serious.**
4. **Risk of bias: No serious.** **Inconsistency: Serious.** Not applicable - no outcomes reported in either arm.; **Indirectness: No serious.** **Imprecision: Very serious.** Not assessable. ; **Publication bias: No serious.**
5. **Risk of bias: Serious.** Inadequate allocation concealment method reporting; **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with continuous oral macrolides; **Publication bias: No serious.**
6. **Risk of bias: No serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no appreciable harm with continuous oral macrolides; **Publication bias: No serious.**
7. **Risk of bias: No serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with continuous oral macrolides; **Publication bias: No serious.**
8. **Risk of bias: No serious.** **Inconsistency: No serious.** **Indirectness: No serious.** **Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with continuous oral macrolides; **Publication bias: No serious.**
9. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Inconsistency: Serious.** Heterogeneity >50% (I² calculated by NICE as 68% using a random effects model); **Indirectness: No serious.** **Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with continuous oral macrolides; **Publication bias: No serious.**

References

Hnin Khin, Nguyen Chau, Carson Kristin V, Evans David J, Greenstone Michael, and Smith Brian J (2015) Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. The Cochrane database of systematic reviews (8), CD001392

2.2.1.4 Nebulised or inhaled antibiotics in adults (subgroup analysis)

GRADE profile - Nebulised or inhaled antibiotics versus placebo or standard care in adults with stable state bronchiectasis

Summary

The evidence review of continuous nebulised or inhaled antibiotics in adults with stable state bronchiectasis is based on 6 placebo-controlled (4 double-blind, 2 open-label) RCTs from 1 systematic review ([Hnin et al. 2015](#)). Antibiotics included: tobramycin (2 studies), gentamicin (1 study), tobramycin and ceftazadime combined (1 study), and ciprofloxacin (2 studies). The duration of antibiotic administration ranged from 4 weeks to 12 months.

Nebulised or inhaled antibiotics did not significantly reduce the number of participants with exacerbations (32.9% compared with 44.4%; RR 0.73, 95% CI 0.44 to 1.22; very low quality evidence), or hospitalisations, compared with placebo or standard care. The number of participants with exacerbations was reported by 4 RCTs of tobramycin, gentamicin or ciprofloxacin (2 studies). Three of these reported a reduction in exacerbations in the treatment group (weighting 95%; only 1 a significant reduction) and 1 reported a non-significant increase in exacerbations in the treatment group (weighting 5%). The trial that demonstrated an increase in exacerbations was a small trial (n=74) of nebulised tobramycin in people who cultured positive for *Pseudomonas aeruginosa*. However, another trial of inhaled ciprofloxacin in people with *Pseudomonas aeruginosa* found a non-significant decrease in exacerbations compared with placebo.

This same trial of nebulised tobramycin compared with placebo reported a significant increase in the adverse event of dyspnoea, and a non-significant increase in wheeze and chest pain, in the treatment group. There was no significant difference in other adverse events, no difference in the number of withdrawals due to intolerable side effects, and no difference in the emergence of resistance.

No systematic reviews or RCTs were identified that investigated nebulised antibiotics in children or young people with stable state bronchiectasis.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo or standard care	Nebulised or inhaled antibiotics		
Number of participants with exacerbations Importance: Critical	Relative risk 0.73 (CI 95% 0.44 - 1.22) Based on data from 294 patients in 4 studies	444 per 1000	324 per 1000	Very Low Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision ¹	We are uncertain whether nebulised or inhaled antibiotics increase or decrease number of participants with exacerbations
		Difference: 120 fewer per 1000 (CI 95% 249 fewer - 98 more)			
Hospitalisations Importance: Critical	Relative risk 0.65 (CI 95% 0.10 - 4.15) Based on data from 213 patients in 3 studies	119 per 1000	77 per 1000	Very Low Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision ²	We are uncertain whether nebulised or inhaled antibiotics increase or decrease hospitalisations
		Difference: 42 fewer per 1000 (CI 95% 107 fewer - 375 more)			
Withdrawals (intolerable side effects) Importance: Critical	Relative risk 0.96 (CI 95% 0.61 - 1.51) Based on data from 317 patients in 5 studies	176 per 1000	169 per 1000	Very Low Due to serious risk of bias, Due to very serious imprecision ³	We are uncertain whether nebulised or inhaled antibiotics increase or decrease withdrawals due to intolerable side effects
		Difference: 7 fewer per 1000 (CI 95% 69 fewer - 90 more)			

Emergence of resistance	Relative risk 2.45 (CI 95% 0.47 - 12.82) Based on data from 252 patients in 4 studies	47 per 1000	115 per 1000	Very Low Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision ⁴	We are uncertain whether nebulised or inhaled antibiotics increase, or have no effect on, emergence of resistance
Importance: Critical		Difference: 68 more per 1000 (CI 95% 25 fewer - 556 more)			
Adverse event - wheeze	Relative risk 13.00 (CI 95% 0.76 - 222.75) Based on data from 74 patients in 1 study	13 per 1000	169 per 1000	Low Due to serious inconsistency, Due to serious imprecision ⁵	Nebulised or inhaled antibiotics may have little or no effect on wheeze
Importance: Critical		Difference: 156 more per 1000 (CI 95% 3 fewer - 2883 more)			
Adverse event - dyspnoea	Relative risk 4.00 (CI 95% 1.23 - 13.02) Based on data from 74 patients in 1 study	81 per 1000	324 per 1000	Low Due to serious imprecision, Due to serious inconsistency ⁶	Nebulised or inhaled antibiotics may increase dyspnoea
Importance: Critical		Difference: 243 more per 1000 (CI 95% 19 more - 974 more)			
Adverse event - chest pain or palpitations	Relative risk 15.00 (CI 95% 0.89 - 253.47) Based on data from 74 patients in 1 study	13 per 1000	195 per 1000	Low Due to serious inconsistency, Due to serious imprecision ⁷	Nebulised or inhaled antibiotics may have little or no effect on chest pain or palpitations
Importance: Critical		Difference: 182 more per 1000 (CI 95% 1 fewer - 3282 more)			
Adverse event - increased cough	Relative risk 0.54 (CI 95% 0.03 - 10.52) Based on data from 198 patients in 2 studies	139 per 1000	75 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ⁸	We are uncertain whether nebulised or inhaled antibiotics made a difference to increased cough
Importance: Critical		Difference: 64 fewer per 1000 (CI 95% 135 fewer - 1323 more)			
Adverse event - nausea	Relative risk 9.45 (CI 95% 0.54 - 164.49) Based on data from 39 patients in 1 study	24 per 1000	227 per 1000	Very Low Due to serious risk of bias, Due to very serious imprecision, Due to serious inconsistency ⁹	We are uncertain whether nebulised or inhaled antibiotics increase or decrease nausea
Importance: Critical		Difference: 203 more per 1000 (CI 95% 11 fewer - 3924 more)			
Adverse event - hemoptysis	Relative risk 1.26 (CI 95% 0.39 - 4.09) Based on data from 198 patients in 2 studies	50 per 1000	63 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision, Due to serious risk of bias ¹⁰	We are uncertain whether nebulised or inhaled antibiotics increase or decrease hemoptysis
Importance: Critical		Difference: 13 more per 1000 (CI 95% 31 fewer - 155 more)			
Adverse event - bronchospasm		52 per 1000	105 per 1000	Very Low	We are uncertain whether nebulised or

Importance: Critical	Relative risk 2.01 (CI 95% 0.61 - 6.63) Based on data from 189 patients in 2 studies	Difference: 53 more per 1000 (CI 95% 20 fewer - 293 more)		Due to serious risk of bias, Due to very serious imprecision ¹¹	inhaled antibiotics increase or decrease bronchospasm
Deaths Importance: Critical	Relative risk 1.49 (CI 95% 0.13 - 17.76) Based on data from 205 patients in 3 studies	9 per 1000	13 per 1000	Very Low Due to very serious risk of bias, Due to very serious imprecision ¹²	There were too few deaths, to determine whether nebulised or inhaled antibiotics made a difference
<ol style="list-style-type: none"> Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; Inconsistency: Serious. Heterogeneity >50% (I2 calculated by NICE as 65% using a random effects model); Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit with nebulised/ inhaled antibiotics; Publication bias: No serious. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Incomplete data and/or large loss to follow up; Inconsistency: Serious. The direction of the effect is not consistent between the included studies, The magnitude of statistical heterogeneity was high, with I²: 67%.; Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised/ inhaled antibiotics; Publication bias: No serious. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias; Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised/ inhaled antibiotics; Publication bias: No serious. Risk of bias: Serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; Inconsistency: Serious. Heterogeneity >50% (I2 calculated by NICE as 55% using a random effects model); Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised/ inhaled antibiotics; Publication bias: No serious. Risk of bias: No serious. Inconsistency: Serious. Not applicable - single RCT.; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with inhaled/ nebulised antibiotics; Publication bias: No serious. Risk of bias: No serious. Inconsistency: Serious. Not applicable - single RCT.; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no appreciable harm with inhaled/nebulised antibiotics; Publication bias: No serious. Risk of bias: No serious. Inconsistency: Serious. Not applicable - single RCT.; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised or inhaled antibiotics; Publication bias: No serious. Risk of bias: No serious. Inconsistency: Serious. Heterogeneity >50% (I2 calculated by NICE as 76% using a random effects model); Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised or inhaled antibiotics; Publication bias: No serious. Risk of bias: Serious. Selective outcome reporting; Inconsistency: Serious. Not applicable - single RCT.; Indirectness: No serious. Imprecision: Very serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised or inhaled antibiotics; Publication bias: No serious. Risk of bias: Serious. Random sequence generation and allocation concealment method not reported. ; Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious. At a minimal 					

important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised or inhaled antibiotics; **Publication bias: No serious.**

11. **Risk of bias: Serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Selective outcome reporting; **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised or inhaled antibiotics; **Publication bias: No serious.**
12. **Risk of bias: Very serious.** Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Inconsistency: No serious. Indirectness: No serious. Imprecision: Very serious.** Non-significant effect, 95% CI of RR crosses null. ; **Publication bias: No serious.**

References

Bilton Diana, Henig Noreen, Morrissey Brian, and Gotfried Mark (2006) Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest* 130(5), 1503-10

2.2.1.5 Nebulised aztreonam

GRADE profile - Nebulised aztreonam versus placebo in adults with stable state bronchiectasis

Summary

The evidence review for nebulised aztreonam is based on 1 systematic review ([Barker et al. 2014](#)) of 2 placebo-controlled, double-blind RCTs in adults with stable state bronchiectasis (AIR-BX1: n=266 and AIR-BX2: n=274) . Participants were randomised to receive two 4-week courses of 75 mg nebulised aztreonam three times a day with a 4-week follow-up period in-between or two 4-week courses of nebulised placebo.

All participants had a history of target Gram-negative organisms (about 80% had *Pseudomonas aeruginosa*) assessed by positive sputum or bronchoscopic culture. The presence of *Haemophilus influenzae* alone did not meet the inclusion criteria. In the previous year, between 35% and 40% of participants had experienced no exacerbations, and between 14% and 21% had experienced 3 or more exacerbations.

There was no significant difference between nebulised aztreonam and placebo in the time to first exacerbation in either trial at 16 weeks (AIR-BX1: HR 1.26, 95% CI 0.79 to 1.99; low quality evidence) and AIR-BX2: HR 1.23, 95% CI 0.80 to 1.91; low quality evidence). There was also no significant difference in the number of participants experiencing an exacerbation between nebulised aztreonam and placebo. In AIR-BX1, 28.4% of the aztreonam group had an exacerbation compared with 26.5% of the placebo group (RR 1.07, 95% CI 0.72 to 1.58; very low quality evidence). In AIR-

BX2 this was 31.6% compared with 27.5% (RR 1.15, 95% CI 0.80 to 1.66; low quality evidence).

Exacerbation was defined as an acute worsening of bronchiectasis with at least 3 major or at least 2 major and 2 minor criteria. Major criteria were defined as: increased sputum production, change in sputum colour, dyspnoea and cough. Minor criteria were: fever (>38°C), increased malaise or fatigue, forced expiratory volume in 1 second or forced vital capacity reduction of more than 10% from baseline, and new or increased haemoptysis.

One trial reported significant increases for aztreonam compared with placebo in serious adverse events (RR 2.12, 95% CI 1.15 to 3.91; low quality evidence), adverse events leading to study drug discontinuation (RR 3.69, 95% CI 1.76 to 7.76; moderate quality evidence) and dyspnoea (RR 1.55, 95% CI 1.18 to 2.04; low quality evidence).

No systematic reviews or RCTs were identified that investigated nebulised azteronam in children or young people with stable state bronchiectasis.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo	Aztreonam		
Time to first exacerbation (AIR-BX1) Importance: Critical	Hazard ratio 1.26 (CI 95% 0.79 - 1.99) Based on data from 266 patients in 1 study			Low Due to serious inconsistency, Due to serious imprecision ¹	Aztreonam may have little or no effect on time to first exacerbation
Time to first exacerbation (AIR-BX2) Importance: Critical	Hazard ratio 1.23 (CI 95% 0.80 - 1.91) Based on data from 274 patients in 1 study			Low Due to serious inconsistency, Due to serious imprecision ²	Aztreonam may have little or no effect on time to first exacerbation
Number of participants with an exacerbation (AIR-BX1) Importance: Critical	Relative risk 1.07 (CI 95% 0.72 - 1.58) Based on data from 266 patients in 1 study	265 per 1000	284 per 1000 Difference: 19 more per 1000 (CI 95% 74 fewer - 154 more)	Very Low Due to serious inconsistency, Due to very serious imprecision ³	We are uncertain whether aztreonam increases or decreases exacerbations
Number of participants with an exacerbation (AIR-BX2) Importance: Critical	Relative risk 1.15 (CI 95% 0.80 - 1.66) Based on data from 274 patients in 1 study	275 per 1000	316 per 1000 Difference: 41 more per 1000 (CI 95% 55 fewer - 181 more)	Low Due to serious inconsistency, Due to serious imprecision ⁴	Aztreonam may have little or no effect on exacerbations

Any adverse event (AIR-BX1) Importance: Critical	Relative risk 1.08 (CI 95% 1.00 - 1.16)	886 per 1000	957 per 1000	Moderate Due to serious inconsistency ⁵	Aztreonam probably has little or no effect on adverse events
	Based on data from 266 patients in 1 study	Difference: 71 more per 1000 (CI 95% 0 fewer - 142 more)			
Any adverse event (AIR-BX2) Importance: Critical	Relative risk 1.07 (CI 95% 0.98 - 1.16)	861 per 1000	921 per 1000	Moderate Due to serious inconsistency ⁶	Aztreonam probably has little or no effect on adverse events
	Based on data from 272 patients in 1 study	Difference: 60 more per 1000 (CI 95% 17 fewer - 138 more)			
Serious adverse event (AIR-BX1) Importance: Critical	Relative risk 2.12 (CI 95% 1.15 - 3.91)	98 per 1000	208 per 1000	Low Due to serious inconsistency, Due to serious imprecision ⁷	Aztreonam may increase serious adverse events slightly
	Based on data from 266 patients in 1 study	Difference: 110 more per 1000 (CI 95% 15 more - 285 more)			
Serious adverse event (AIR-BX2) Importance: Critical	Relative risk 1.14 (CI 95% 0.61 - 2.14)	117 per 1000	133 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ⁸	We are uncertain whether aztreonam increases or has no effect on serious adverse events
	Based on data from 272 patients in 1 study	Difference: 16 more per 1000 (CI 95% 46 fewer - 133 more)			
Adverse event leading to study drug discontinuation (AIR-BX1) Importance: Critical	Relative risk 3.69 (CI 95% 1.76 - 7.76)	61 per 1000	225 per 1000	Moderate Due to serious inconsistency ⁹	Aztreonam probably increases adverse events leading to study drug discontinuation
	Based on data from 266 patients in 1 study	Difference: 164 more per 1000 (CI 95% 46 more - 412 more)			
Adverse events leading to study drug discontinuation (AIR-BX2) Importance: Critical	Relative risk 1.88 (CI 95% 0.78 - 4.58)	51 per 1000	96 per 1000	Low Due to serious inconsistency, Due to serious imprecision ¹⁰	Aztreonam may have little or no effect on adverse events leading to study drug discontinuation
	Based on data from 272 patients in 1 study	Difference: 45 more per 1000 (CI 95% 11 fewer - 183 more)			
Adverse event - dyspnoea (AIR-BX1) Importance: Critical	Relative risk 1.55 (CI 95% 1.18 - 2.04)	356 per 1000	552 per 1000	Low Due to serious inconsistency, Due to serious imprecision ¹¹	Aztreonam may increase dyspnoea slightly
	Based on data from 266 patients in 1 study	Difference: 196 more per 1000 (CI 95% 64 more - 370 more)			
Adverse event - dyspnoea (AIR-BX2) Importance: Critical	Relative risk 1.08 (CI 95% 0.78 - 1.49)	343 per 1000	370 per 1000	Low Due to serious inconsistency, Due to serious imprecision ¹²	Aztreonam may have little or no effect on dyspnoea
	Based on data from 272 patients in 1 study	Difference: 27 more per 1000 (CI 95% 75 fewer - 168 more)			

1. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised aztreonam; **Publication bias: No serious.**
2. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with nebulised aztreonam; **Publication bias: No serious.**
3. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT.; **Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with aztreonam.; **Publication bias: No serious.**
4. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT.; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with aztreonam; **Publication bias: No serious.**
5. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT.; **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
6. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT.; **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
7. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with aztreonam; **Publication bias: No serious.**
8. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT.; **Indirectness: No serious. Imprecision: Very serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with aztreonam; **Publication bias: No serious.**
9. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT. ; **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**
10. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with aztreonam; **Publication bias: No serious.**
11. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with aztreonam; **Publication bias: No serious.**
12. **Risk of bias: No serious. Inconsistency: Serious.** Not applicable - single RCT; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable harm with aztreonam; **Publication bias: No serious.**

References

Barker Alan F, O'Donnell Anne E, Flume Patrick, Thompson Philip J, Ruzi Jonathan D, de Gracia , Javier , Boersma Wim G, De Soyza , Anthony , Shao Lixin, Zhang Jenny, Haas Laura, Lewis Sandra A, Leitzinger Sheila, Montgomery A Bruce, McKevitt Matthew T, Gossage David, Quittner Alexandra L, and O'Riordan Thomas G (2014) Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. *The Lancet. Respiratory medicine* 2(9), 738-49

2.2.1.6 Nebulised colistimethate sodium

GRADE profile - Nebulised colistimethate sodium versus placebo in adults with chronic *Pseudomonas aeruginosa* infection who had been treated with an antipseudomonal antibiotic for an exacerbation of bronchiectasis in the last 21 days

Summary

The evidence for nebulised colistimethate sodium was added to the evidence review following stakeholder consultation, when an additional RCT, [Haworth et al. 2014](#) was highlighted.

The evidence review for nebulised colistimethate sodium is based on 1 placebo-controlled, double-blind RCT in adults with bronchiectasis who had chronic *Pseudomonas aeruginosa* infection and had been treated with an antipseudomonal antibiotic for an exacerbation in the last 21 days (n=144). Participants were randomised to receive either nebulised colistimethate sodium 1 million IU twice a day (n=73) or nebulised 0.45% saline twice a day (n=71) for up to 6 months.

There was no significant difference between nebulised colistimethate sodium and placebo in the time to first exacerbation in the intention-to-treat population (median time [25% quartile] 165 [42] days in the colistimethate sodium group compared with 111 [52] days in the placebo group, p=0.11). However, there was a significant difference between groups when participants who were at least 81% adherent were analysed (168 [65] days in the colistimethate sodium group compared with 103 [37] days in the placebo group, p=0.038; pre-defined secondary end point, n=106).

There was no significant difference between nebulised colistimethate sodium and placebo in the number of participants who had an exacerbation in the intention-to-treat population (RR 0.83, 95% CI 0.62 to 1.13; low quality evidence) or in the population who were at least 81% adherent (RR 0.73, 95% CI 0.53 to 1.01; low quality evidence, n=106).

There was no significant difference between nebulised colistimethate sodium and placebo in the number of participants experiencing adverse events, serious adverse events or withdrawals due to adverse events.

No systematic reviews or RCTs were identified that investigated nebulised colistimethate sodium in children or young people with.

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty in effect estimates (Quality of evidence)	Plain text summary
		Placebo or standard care	Colistimethate sodium		
Number of people with an exacerbation Importance: Critical	Relative risk 0.83 (CI 95% 0.62 – 1.13) Based on data from 144 patients in 1 study	592 per 1000	491 per 1000	Low Due to serious inconsistency, Due to serious imprecision ¹	Colistimethate sodium may have little or no effect on the number of people with an exacerbation
		Difference: 101 fewer per 1000 (CI 95% 225 fewer – 77 more)			
Number of adherent people with an exacerbation Importance: Critical	Relative risk 0.73 (CI 95% 0.53 – 1.01) Based on data from 106 patients in 1 study	712 per 1000	520 per 1000	Low Due to serious inconsistency, Due to serious imprecision ²	Colistimethate sodium may have little or no effect on the number of adherent people with an exacerbation
		Difference: 192 fewer per 1000 (CI 95% 192 fewer – 7 more)			
Number of people with adverse events Importance: Critical	Relative risk 1.20 (CI 95% 0.91 - 1.59) Based on data from 144 patients in 1 study	535 per 1000	642 per 1000	Low Due to serious inconsistency, Due to serious imprecision ³	Colistimethate sodium may have little or no effect on adverse events
		Difference: 107 more per 1000 (CI 95% 48 fewer - 316 more)			
Number of people with serious adverse events Importance: Critical	Relative risk 1.46 (CI 95% 0.43 – 4.95) Based on data from 144 patients in 1 study	56 per 1000	82 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ⁴	We are uncertain whether colistimethate sodium increases or decreases serious adverse events
		Difference: 26 more per 1000 (CI 95% 32 fewer - 221 more)			
Number of people with adverse events leading to withdrawal Importance: Critical	Relative risk 1.13 (CI 95% 0.40 – 3.21) Based on data from 144 patients in 1 study	85 per 1000	96 per 1000	Very Low Due to serious inconsistency, Due to very serious imprecision ⁵	We are uncertain whether colistimethate sodium increases or decreases adverse events leading to withdrawal
		Difference: 11 more per 1000 (CI 95% 51 fewer - 188 more)			
Time to first exacerbation Importance: Critical	Based on data from 144 patients in 1 study	The median time (25% quartile) to exacerbation was 165 days (42 days) in the colistimethate sodium group and 111 days (52 days) in the placebo group (p=0.11)		Not assessable	Not assessable

Time to first exacerbation in adherent people Importance: Critical	Based on data from 106 patients in 1 study	The median time (25% quartile) to exacerbation was 168 days (65 days) in the colistimethate sodium group and 103 days (37 days) in the placebo group (p=0.038)	Not assessable	Not assessable
<p>¹ Risk of bias: No serious. Inconsistency: Serious. Not assessable ; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with colistimethate sodium; Publication bias: No serious.</p> <p>² Risk of bias: No serious. Inconsistency: Serious. Not assessable ; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with colistimethate sodium; Publication bias: No serious.</p> <p>³ Risk of bias: No serious. Inconsistency: Serious. Not assessable ; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with colistimethate sodium; Publication bias: No serious.</p> <p>⁴ Risk of bias: No serious. Inconsistency: Serious. Not assessable ; Indirectness: No serious. Imprecision: Very Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with colistimethate sodium; Publication bias: No serious.</p> <p>⁵ Risk of bias: No serious. Inconsistency: Serious. Not assessable ; Indirectness: No serious. Imprecision: Serious. At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference or appreciable benefit/harm with colistimethate sodium; Publication bias: No serious.</p>				

References

Haworth Charles S, Foweraker Juliet E, Wilkinson Peter, Kenyon Robert F, and Bilton Diana (2014) Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. American journal of respiratory and critical care medicine 189(8), 975-82

3 Literature search

A range of evidence sources are used to develop antimicrobial prescribing guidelines. These fall into 2 broad categories:

- Evidence identified from the literature search
- Evidence identified from other information sources. Examples of other information sources used are shown in the [interim process guide](#) (2017).

See evidence sources for full details of evidence sources used for this guideline.

A literature search was developed to identify evidence for the effectiveness and safety of interventions for managing acute exacerbations of non-cystic fibrosis bronchiectasis (see [literature search strategy](#) for full details). The literature search identified 1,072 references. These references were screened using their titles and abstracts and 210 full text references were obtained and assessed for relevance. There were 26 full text references of [systematic reviews](#) and [randomised controlled trials](#) (RCTs) assessed as relevant to the guideline review question (see [review protocol](#)). Ten percent of studies were screened to establish inter-rater reliability, and this was within the required threshold of 90%.

The methods for identifying, selecting and prioritising the best available evidence from the literature search are described in the [interim process guide](#). Four of the 26 references were prioritised by the committee as the best available evidence and were included in this evidence review (see [included studies](#)).

The 22 references that were not prioritised for inclusion are listed in [studies not prioritised](#), with reasons for not prioritising the studies. Also see [evidence prioritisation](#) for more information on study selection.

The remaining 184 references were excluded. These are listed in excluded studies with reasons for their exclusion.

See also [study flow diagram](#).

4 Review protocol

Review protocol for acute exacerbation of bronchiectasis (non-cystic fibrosis)

I	Review question	<p>What pharmacological (antimicrobial and non-antimicrobial) interventions are effective in managing an acute exacerbation of bronchiectasis (non-cystic fibrosis)?</p> <p>Following stakeholder consultation amended to:</p> <p>What antimicrobial and non-antimicrobial interventions are effective in treating, and what antimicrobial interventions are effective in preventing, an acute exacerbation of bronchiectasis (non-cystic fibrosis)?</p>	<ul style="list-style-type: none"> antimicrobials include antibiotics non-antimicrobials include analgesia and antipyretics (e.g. paracetamol and ibuprofen), oral corticosteroids (e.g. prednisolone); bronchodilators (beta-2 agonists, anticholinergics and leukotriene receptor antagonists), mucolytics and herbal medicines search will include terms for acute exacerbation of bronchiectasis.
II	Types of review question	Intervention questions will primarily be addressed through the search.	These will, for example, also identify natural history in placebo groups and causative organisms in studies that use laboratory diagnosis, and relative risks of differing management options.
III	Objective of the review	<p>To determine the effectiveness of prescribing and other interventions in managing an infective exacerbation of bronchiectasis (non-cystic fibrosis), in line with the major goals of antimicrobial stewardship. This includes interventions that lead prescribers to:</p> <ul style="list-style-type: none"> optimise outcomes for individuals reduce overuse, misuse or abuse of antimicrobials <p>All of the above will be considered in the context of national antimicrobial resistance patterns where available, if not available committee expertise will be used to guide decision-making.</p>	<p>The secondary objectives of the review of studies will include:</p> <ul style="list-style-type: none"> indications for no or back-up antimicrobials indications for non-antimicrobial interventions antimicrobial choice, optimal dose, duration and route for specified antimicrobial(s) the natural history of the infection identifying subgroups of people who are more

			likely to benefit from antimicrobials.
IV	Eligibility criteria – population/ disease/ condition/ issue/domain	<p>Population: Adults and children (aged 72 hours and older) with an infective exacerbation of bronchiectasis (non-cystic fibrosis).</p> <p>Studies that use for example symptoms or signs (prognosis), clinical diagnosis, imaging, microbiological methods, or laboratory testing of blood for diagnosing the condition.</p>	<p>Subgroups of interest, those:</p> <ul style="list-style-type: none"> • with protected characteristics under the Equality Act 2010. • with chronic conditions (such as high blood pressure, diabetes or heart disease). • at high risk of serious complications because of pre-existing comorbidity[1] • with symptoms and signs suggestive of serious illness and/or complications[2] • younger than 18 years (children) including those with fever and additional intermediate or high risk factors[3] • patient is older than 65 years and older than 80 years[4] • with purulent sputum and exacerbations • with moderate or high severity community acquired pneumonia • with asthma.
V	Eligibility criteria – intervention(s)/ exposure(s)/ prognostic factor(s)	<p>The review will include studies which include:</p> <ul style="list-style-type: none"> • Non-antimicrobial pharmacological interventions[5]. • Antimicrobial pharmacological interventions[6]. <p>For the treatment or prophylaxis of an infective exacerbation of bronchiectasis, as outlined above, in primary, secondary or other care settings (for example walk-in-centres and urgent care) either by prescription or by any other legal means of supply of medicine (for example patient group direction).</p>	Limited to those interventions commonly in use (as agreed by the committee)

VI	Eligibility criteria – comparator(s)/ control or reference (gold) standard	<p>Any other plausible strategy or comparator, including:</p> <ul style="list-style-type: none"> • Placebo or no treatment. • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions. 	
VII	Outcomes and prioritisation	<p>a. Clinical outcomes such as:</p> <ul style="list-style-type: none"> • mortality • infection cure rates (number or proportion of people with resolution of symptoms at a given time point, incidence of escalation of treatment) • time to clinical cure (mean or median time to resolution of illness) • reduction in symptoms (duration or severity) • rate of complications with or without treatment • safety, tolerability, and adverse effects. <p>a. Thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials)</p> <p>b. Changes in antimicrobial resistance patterns, trends and levels as a result of treatment.</p> <p>c. Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction.</p> <p>d. Ability to carry out activities of daily living.</p> <p>e. Service user experience.</p> <p>f. Health and social care related quality of life, including long-term harm or disability.</p> <p>g. Health and social care utilisation (including length of stay, planned and unplanned contacts).</p> <p>The Committee considered which outcomes should be prioritised when multiple outcomes are reported (critical and important outcomes). Additionally, the Committee were asked to consider what clinically important features of study design may be important for this</p>	<p>The committee have agreed that the following outcomes are critical:</p> <ul style="list-style-type: none"> • reduction in symptoms (duration or severity) for example difference in time to substantial improvement • time to clinical cure (mean or median time to resolution of illness) • rate of complications^[7] (including mortality) with or without treatment, including escalation of treatment • health and social care utilisation (including length of stay, ITU stays, planned and unplanned contacts). • thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) <p>The committee have agreed that the following outcomes are important:</p> <ul style="list-style-type: none"> • patient-reported outcomes, such as medicines adherence, patient experience, sickness absence • changes in antimicrobial resistance patterns, trends and levels as a result of treatment

		condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	
VIII	Eligibility criteria – study design	<p>The search will look for:</p> <ul style="list-style-type: none"> • Systematic review of randomised controlled trials (RCTs) • RCTs <p>If insufficient evidence is available progress to:</p> <ul style="list-style-type: none"> • Controlled trials • Systematic reviews of non-randomised controlled trials • Non-randomised controlled trials • Observational and cohort studies • Pre and post intervention studies (before and after) • Time series studies 	Committee to advise the NICE project team on the inclusion of information from other condition specific guidance and on whether to progress due to insufficient evidence.
IX	Other inclusion exclusion criteria	<p>The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include:</p> <ul style="list-style-type: none"> • non-English language papers, studies that are only available as abstracts • in relation to antimicrobial resistance, non-UK papers • bronchiectasis due to cystic fibrosis • maintenance treatment of stable bronchiectasis with exercise, diet, breathing techniques etc. • non-pharmacological interventions, for example physical therapy • vaccinations 	
X	Proposed sensitivity/ sub-group analysis, or meta-regression	<p>The search may identify studies in population subgroups (for example adults, older adults, children (those aged under 18 years of age), and people with co-morbidities or characteristics that are protected under the Equality Act 2010 or in the NICE equality impact assessment). These will be included if studies stratify results by population subgroups, and these categories may enable the production of management recommendations.</p>	

XI	Selection process – duplicate screening/ selection/ analysis	<p>All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above.</p> <p>A randomly selected initial sample of 10% of records will be screened by two reviewers independently. The rate of agreement for this sample will be recorded, and if it is over 90% then remaining references will be screened by one reviewer only. Disagreement will be resolved through discussion.</p> <p>Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved.</p> <p>If large numbers of papers are identified and included at full text, the Committee may consider prioritising the evidence for example, evidence of higher quality in terms of study type or evidence with critical or highly important outcomes.</p>	
XII	Data management (software)	<p>Data management will be undertaken using EPPI-reviewer software. GRADEpro will be used to assess the quality of evidence for each outcome.</p>	
XIII	Information sources – databases and dates	<p>The following sources will be searched:</p> <ul style="list-style-type: none"> • Cochrane Central Register of Controlled Trials (CENTRAL) via Wiley • Cochrane Database of Systematic Reviews (CDSR) via Wiley • Database of Abstracts of Effectiveness (DARE) via Wiley – legacy, last updated April 2015 • Embase via Ovid • Health Technology Assessment (HTA) via Wiley • MEDLINE via Ovid • MEDLINE-in-Process via Ovid <p>The search strategy will be developed in MEDLINE and then adapted or translated as appropriate for the other sources, taking into account their size, search functionality and subject coverage.</p> <p>Database functionality will be used, where available, to exclude:</p> <ul style="list-style-type: none"> • non-English language papers 	

		<ul style="list-style-type: none"> • animal studies • editorials, letters, news items, case reports and commentaries • conference abstracts and posters • theses and dissertations • duplicates. <p>Date limits will be applied to restrict the search results to:</p> <ul style="list-style-type: none"> • studies published from 2006 to the present day <p>The results will be downloaded in the following mutually exclusive sets:</p> <ul style="list-style-type: none"> • Systematic reviews and meta-analysis • Randomised controlled trials • Observational and comparative studies • Other results <p>See appendix B for further details on the search strategy.</p> <p>Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening.</p>	
XV	Author contacts	<p>Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content</p> <p>Email: infections@nice.org.uk</p>	
XVI	Highlight if amendment to previous protocol	For details please see the interim process guide (2017).	
XVII	Search strategy – for one database	For details see appendix C.	
XVIII	Data collection process – forms/duplicate	GRADE profiles will be used, for details see appendix H.	
XIX	Data items – define all variables to be collected	GRADE profiles will be used, for details see appendix H.	
XX	Methods for assessing bias	Standard study checklists were used to critically appraise individual studies. For details please see the interim process	

	at outcome/ study level	guide (2017). The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/	
XXI	Criteria for quantitative synthesis (where suitable)	For details please see the interim process guide (2017).	
XXII	Methods for analysis – combining studies and exploring (in)consistency	For details please see the interim process guide (2017).	
XXIII	Meta-bias assessment – publication bias, selective reporting bias	For details please see the interim process guide (2017).	
XXIV	Assessment of confidence in cumulative evidence	For details please see the interim process guide (2017).	
XXV	Rationale/ context – Current management	For details please see the interim process guide (2017).	
XXVI	Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE and chaired by Dr Tessa Lewis in line with the interim process guide (2017). Staff from NICE undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.	
XXVII	Sources of funding/support	Developed and funded by NICE.	

XXVII I	Name of sponsor	Developed and funded by NICE.	
XXIX	Roles of sponsor	NICE funds and develops guidelines for those working in the NHS, public health, and social care in England.	
<p>[1] significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, and young children who were born prematurely</p> <p>[2] Including pneumonia, heart, lung, kidney, liver or neuromuscular disease, or immunosuppression</p> <p>[3] Outlined in more detail in CG160 Fever in under 5s: assessment and initial management</p> <p>[4] hospitalisation in previous year; type 1 or type 2 diabetes, history of congestive heart failure, current use of oral glucocorticoids.</p> <p>[5] Non-antimicrobial pharmacological interventions include: analgesics and bronchodilators</p> <p>[6] Antimicrobial pharmacological interventions include: delayed (back-up) prescribing, standby or rescue therapy, narrow or broad spectrum, single, dual or triple therapy, escalation or de-escalation of treatment. Antibiotics included in the search include those named in current guidance (plus the class to which they belong) plus other antibiotics agreed by the committee</p> <p>[7] These would include but are not limited to more common complications e.g. chronic bacterial colonization and haemoptysis</p>			

5 Evidence prioritisation

Key questions	Included studies		Non-prioritised studies	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Which non-antimicrobial pharmacological interventions are effective?				
Non-antimicrobial interventions for treating acute exacerbations	-	-	-	-
Which antibiotic prescribing strategies are effective (including back-up antibiotics)?				
Antibiotic prescribing strategies	-	-	-	-
Is an antibiotic effective?				
Prolonged antibiotics versus placebo	Hnin et al. 2015 Barker et al. 2014	Haworth et al. 2014	Fan et al. 2015 Gao et al. 2014 Wu et al. 2014 Zhuo et al. 2014 Magis-Escurra et al. 2015 Brodth et al. 2014 Xu et al. 2016 Yang et al. 2016	Altenburg et al. 2013 Masekela et al. 2013 Serisier et al. 2013 (ORBIT) Serisier et al. 2013 (BLESS) Rogers et al. 2014 Wong et al. 2012 Valery et al. 2013 Murray et al. 2011 Antoniou et al. 2011 Chalmers et al. 2012 Lourdesamy et al. 2014 Orriols et al. 2015 Yalcin et al. 2006
Short-course antibiotics versus placebo	-	-	Wurzel et al. 2011	-
Which people are most likely to benefit from an antibiotic?				
Children	-	-	-	-
Adults	-	-	-	-

Which antibiotic is most effective?				
Antibiotics versus different antibiotics studies	-	Bilton et al. 2006	-	-
What is the optimal dose, duration and route of administration of antibiotic?				
Dosage	-	-	-	-
Course length	-	-	-	-
Route of administration studies	-	-	-	-

6 Literature search strategy

Search format

The main search strategy will take the following format:

- Bronchiectasis
- AND (Named Antibiotics OR Classes of Antibiotics OR Pharma interventions OR Honey OR Herbal Medicines OR Drinking Fluids OR Prescribing Strategies OR Self Care)
- AND (Systematic Reviews OR Randomised Controlled Trials OR Observational Studies)
- AND Limits

The strategy includes a top up search for the following terms:

- Bronchiectasis
- AND General term “Antibiotics”
- AND Systematic Reviews

Outline of the search strategy

Main concepts	Concept	Proposed search terms
Condition	Bronchiectasis	Bronchiectasis/ (bronchiect* or bronchoect*).ti,ab ((suppurative* or dilat*) adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ti,ab.
Named Antibiotics	Amoxicillin	Amoxicillin/ (Amoxicillin* or Amoxycillin* or Amoxil*).ti,ab.
	Amoxicillin and a macrolide dual therapy	-
	Ampicillin	Ampicillin/ Ampicillin*.ti,ab
	Azithromycin	Azithromycin/ (Azithromycin* or Azithromicin* or Zithromax*).ti,ab
	Aztreonam	Aztreonam/ (Aztreonam* or Azactam*).ti,ab
	Benzylpenicillin sodium	Penicillin G/ (Benzylpenicillin* or "Penicillin G").ti,ab
	Beta-lactamase stable beta-lactam	-

Main concepts	Concept	Proposed search terms
	Cefaclor	Cefaclor/ (Cefaclor* or Distaclor* or Keftid*).ti,ab
	Cefixime	Cefixime/ (Cefixime* or Suprax*).ti,ab
	Cefotaxime	Cefotaxime/ Cefotaxime*.ti,ab.
	Ceftaroline fosamil	(Ceftaroline* or Zinforo*).ti,ab
	Ceftazidime	Ceftazidime/ (Ceftazidime* or Fortum* or Tazidime*).ti,ab
	Ceftobiprole No Mesh	(Ceftobiprole* or Zevtera*).ti,ab
	Ceftolozane-tazobactam	(Ceftolozane* or Tazobactam* or Zerbaxa*).ti,ab
	Ceftriaxone	Ceftriaxone/ (Ceftriaxone* or Rocephin* or Rocefin*).ti,ab
	Cefuroxime	Cefuroxime/ (Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab
	Chloramphenicol	Chloramphenicol/ (Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab
	Ciprofloxacin	Ciprofloxacin/ (Ciprofloxacin* or Ciproxin*).ti,ab
	Clarithromycin	Clarithromycin/ (Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab
	Clindamycin	Clindamycin/ (Clindamycin* or Dalacin* or Zindaclin*).ti,ab
	Co-amoxiclav	Amoxicillin-Potassium Clavulanate Combination/ (Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab
	Co-trimoxazole	Trimethoprim, Sulfamethoxazole Drug Combination/ (Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab
	Colistin	Colistin/ (Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab.

Main concepts	Concept	Proposed search terms
	Doxycycline	Doxycycline/ (Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab
	Ertapenem	(Ertapenem* or Invanz*).ti,ab
	Erythromycin	Erythromycin/ Erythromycin Estolate/ Erythromycin Ethylsuccinate/ (Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab
	Fosfomicin	Fosfomicin/ (Fosfomicin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab
	Flucloxacillin	Floxacillin/ (Floxacillin* or Flucloxacillin*).ti,ab.
	Fluoroquinolone	-
	Gentamicin	Gentamicins/ (Gentamicin* or Gentamycin* or Cidomycin*).ti,ab
	Imipenem	Imipenem/ (Imipenem* or Primaxin*).ti,ab
	Levofloxacin	Levofloxacin/ (Levofloxacin* or Evoxil* or Tavanic*).ti,ab.
	Linezolid	Linezolid/ (Linezolid* or Zyvox*).ti,ab
	Meropenem	(Meropenem*).ti,ab
	Moxifloxacin	(Moxifloxacin* or Avelox*).ti,ab
	Ofloxacin	Ofloxacin/ (Ofloxacin* or Tarivid*).ti,ab
	Piperacillin with Tazobactam	Piperacillin/ (Piperacillin* or Tazobactam* or Tazocin*).ti,ab
	Rifampicin	Rifampin/ (Rifampicin* or Rifampin* or Rifadin* or Rimactane*).ti,ab
	Teicoplanin	Teicoplanin/ (Teicoplanin* or Targocid*).ti,ab
	Telavancin	(Telavancin* or Vibativ*).ti,ab
	Temocillin	(Temocillin* or Negaban*).ti,ab
	Tigecycline	(Tigecycline* or Tygacil*).ti,ab
	Vancomycin	Vancomycin/ (Vancomycin* or Vancomycin* or Vancocin*).ti,ab

Main concepts	Concept	Proposed search terms
Classes of Antibiotics	Aminoglycoside	exp Aminoglycosides/ Aminoglycoside*.ti,ab
	Antipseudomonal penicillin	exp Penicillins/ Penicillin*.ti,ab
	Beta-lactamase	exp beta-Lactamases/ ("beta Lactamase*" or betaLactamase* or "beta-Lactamase*").ti,ab exp beta-Lactamase inhibitors/ (("beta Lactamase*" or betaLactamase*) adj3 (inhibitor* or antagonist*).ti,ab
	Beta-lactam (stable)	beta-Lactams/ ("beta-Lactam" or betaLactam or "beta Lactam" or "beta-Lactams" or betaLactams or "beta Lactams").ti,ab
	Carbapenems	exp Carbapenems/ Carbapenem*.ti,ab
	Cephalosporin	exp Cephalosporins/ Cephalosporin*.ti,ab
	Fluoroquinolone	exp Fluoroquinolones/ Fluoroquinolone*.ti,ab
	Macrolides	exp Macrolides/ macrolide*.ti,ab
	Polymyxins	Polymyxins/ Polymyxin*.ti,ab
	Quinolones	exp Quinolones/ Quinolone*.ti,ab
	Tetracycline	exp Tetracyclines/ Tetracycline*.ti,ab
Pharma interventions	Analgesics	analgesics/ exp analgesics, non-narcotic/ analgesics, short-acting/ antipyretics/ (analgesic* or antipyretic*).ti,ab
	Paracetamol	Acetaminophen/ (paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab

Main concepts	Concept	Proposed search terms
	Anticholinergics	Cholinergic antagonists/ (Anticholinergic* or "Anti-cholinergic*" or "Anti cholinergic*" or Antimuscarinic* or Anti muscarinic* or Anti-muscarinic*).ti,ab ((cholinergic* or acetylcholine* or cholinolytic* or muscarinic*) adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab
	Beta-2 agonists	Adrenergic beta-2 Receptor Agonists/ (("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. Albuterol/ (Salbutamol* or Albuterol* or Salbulin* or Ventolin* or Salamol*).ti,ab
	Bronchodilators	Bronchodilator Agents/ (Bronchodilator* or broncholytic* or bronchial dilat* or bronchodilating* or bronchodilatant*).ti,ab
	Codeine and Pholcodine	exp Codeine/ (Codeine* or Pholcodine* or Covonia* or Galenphol* or Pavacol* or Galcodine*).ti,ab.
	Corticosteroids	Adrenal Cortex Hormones/ (Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab
	Cough mixtures Non-prescription drugs Antitussive agents Anti-histamines Demulcents Glycerol Menthol Honey and Lemon	Nonprescription Drugs/ (non prescription* or nonprescription* or otc or "over the counter*" or "over-the-counter*").ti,ab Antitussive Agents/ (Antitussive*).ti,ab (cough* adj3 (suppressant* or mixture* or syrup* or medicine* or medicinal* or product or products or remedies* or remedy*)).ti,ab exp Histamine Antagonists/ Antazoline/ Brompheniramine/ Chlorpheniramine/ Cinnarizine/ Cyproheptadine/ Diphenhydramine/ Doxylamine/ Ergotamine/ Hydroxyzine/ Ketotifen/ Pizotyline/

Main concepts	Concept	Proposed search terms
		Promethazine/ Trimeprazine/ Triprolidine/ (histamin* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab (antihistamin* or anti-histamin* or Alimemazine* or Trimeprazine* or Antazoline* or Brompheniramine* or Chlorpheniramine* or Chlorphenamine* or Cinnarizine* or Stugeron* or Cyproheptadine* or Periactin* or Diphenhydramine* or Doxylamine* or Ergotamine* or Migril* or Hydroxyzine* or Atarax* or Ketotifen* or Zaditen* or Promethazine* or Phenergan* or Sominex* or Pizotifen* or Pizotiline* or Triprolidine* or Acrivastine*).ti,ab Demulcents/ (demulcent* or mucoprotective* or muco protective* or Linctus*).ti,ab Glycerol/ (Glycerol* or Glycerine*).ti,ab Menthol/ (menthol*).ti,ab Honey/ Apitherapy/ (honey* or lemon*).ti,ab
	Dextromethorphan	Dextromethorphan/ (Dextromethorphan*).ti,ab
	Prednisolone	exp Prednisolone/ (Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab
	Non-steroidal anti-inflammatory drugs	Anti-Inflammatory Agents, Non-Steroidal/ (nsaid*).ti,ab ((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab
	Ibuprofen	Ibuprofen/ (ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab
	Leukotriene receptor antagonists	Leukotriene Antagonists/ (leukotriene* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab. (Montelukast*).ti,ab (Zafirlukast* or Accolate*).ti,ab

Main concepts	Concept	Proposed search terms
	Mucolytics	exp Expectorants/ exp Guaifenesin/ Ipecac/ (expectorant* or mucolytic* or guaifenesin* or ipecac* or ipecacuanha*).ti,ab Mannitol/ (Mannitol* or Osmohale* or Bronchitol*).ti,ab (Dornase alfa* or Dornase alpha* or Pulmozyme*).ti,ab.
Herbal remedies	Herbal medicines Pelargonium (kaloba) Echinacea Japonica Thyme Eucalyptus Forsythiae Liquorice Andrographis	Drugs, Chinese Herbal/ Plants, Medicinal/ exp Geraniaceae/ Echinacea/ Fallopia Japonica/ Thymus Plant/ Eucalyptus/ Forsythia/ exp Glycyrrhiza/ Andrographis/ (herb* or Geraniaceae* or Pelargonium* or Geranium* or Kaloba* or Echinacea* or Coneflower* or Japonica* or Knotweed* or Thyme* or Thymus* or Eucalyptus* or Forsythia* or Forsythiae* or Goldenbell* or Lian Qiao* or Glycyrrhiza* or Licorice* or Liquorice* or Andrographis*).ti,ab ((medicine* or medical* or medicinal* or product or products or remedies* or remedy*) adj3 (plant* or plants or root or roots or flower or flowers or bark or barks or seed or seeds or shrub or shrubs or botanic*)).ti,ab
Drinking Fluids	Fluid therapy	Drinking/ Drinking Behavior/ Fluid therapy/
	Drinking water, beverages, fluids or liquids	exp Beverages/ ((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat* or therap*)).ti,ab
Prescribing Strategies	Active surveillance	watchful waiting/
	No intervention	"no intervention".ti,ab
	Watchful waiting	(watchful* adj2 wait*).ti,ab. (wait adj2 see).ti,ab (expectant* adj2 manage*).ti,ab (active* adj2 surveillance*).ti,ab

Main concepts	Concept	Proposed search terms
	Prescribing times Delayed treatment	<p>((prescription* or prescrib*) adj4 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv*)).ti,ab</p> <p>((misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*) adj4 (bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*")).ti,ab</p> <p>((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.</p> <p>anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/</p> <p>(antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab.</p> <p>(delay* or defer* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or (prescribing adj strateg*) or "red flag*").ti,ab</p> <p>Inappropriate prescribing/</p>
Self Care	Self management	<p>Self Care/</p> <p>Self medication/</p> <p>((self or selves or themsel*) adj4 (care or manag*)).ti,ab</p>
Systematic Reviews	Meta analysis Systematic Reviews Reviews	Standard search filter
Randomised Controlled Trials	Controlled Clinical Trials Cross over studies Randomised controlled trials (rcts)	Standard search filter
Observational Studies	Case-Control Studies Cohort Studies Controlled Before-After Studies Cross-Sectional Studies Epidemiologic Studies Observational Study	Standard search filter

Main concepts	Concept	Proposed search terms
Limits	Exclude Animal studies Exclude letters, editorials and letters Limit date to 2006-Current	Standard search limits

Number of hits to be retrieved

	No. of hits in MEDLINE	Position in the strategy
Search with limits and Systematic Reviews	785	Line 236
Search with limits and RCTs (not SRs)	119	Line 255
Search with limits and Observational Studies (not SRs or RCTs)	191	Line 278
Search with limits (without SRs, RCTs, Observational)	206	Line 279
Total for screening	1301	

Key to search operators

/	Medical Subject Heading (MeSH) term
Exp	Explodes the MeSH terms to retrieve narrower terms in the hierarchy
.ti	Searches the title field
.ab	Searches the abstract field
*	Truncation symbol (searches all word endings after the stem)
adj n	Adjacency operator to retrieve records containing the terms within a specified number (n) of words of each other

MEDLINE search strategy

Database(s): Ovid MEDLINE(R) 1946 to October Week 3 2017, Ovid MEDLINE(R) Epub Ahead of Print October 25, 2017, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations October 25, 2017, Ovid MEDLINE(R) Daily Update October 25, 2017

Search Strategy:

#	Searches	Results
1	Bronchiectasis/	7726
2	(bronchiect* or bronchoect*).ti,ab.	8845

#	Searches	Results
3	((suppurative* or dilat*) adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ti,ab.	4250
4	or/1-3	15626
5	limit 4 to yr="2006 -Current"	5600
6	limit 5 to english language	4957
7	Animals/ not (Animals/ and Humans/)	4647558
8	6 not 7	4731
9	limit 8 to (letter or historical article or comment or editorial or news or case reports)	1083
10	8 not 9	3648
11	anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/	909485
12	(antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*").ti,ab.	434507
13	or/11-12	1096889
14	Amoxicillin/	9366
15	(Amoxicillin* or Amoxycillin* or Amoxil*).ti,ab.	16436
16	Ampicillin/	13810
17	Ampicillin*.ti,ab.	22052
18	Azithromycin/	4776
19	(Azithromycin* or Azithromicin* or Zithromax*).ti,ab.	7229
20	Aztreonam/	1438
21	(Aztreonam* or Azactam*).ti,ab.	2954
22	Penicillin G/	9348
23	(Benzylpenicillin* or "Penicillin G").ti,ab.	8208
24	Cefaclor/	881
25	(Cefaclor* or Distaclor* or Keftid*).ti,ab.	1741
26	Cefixime/	773
27	(Cefixime* or Suprax*).ti,ab.	1572
28	Cefotaxime/	5575
29	Cefotaxime*.ti,ab.	8129
30	(Ceftaroline* or Zinforo*).ti,ab.	583
31	Ceftazidime/	3797
32	(Ceftazidime* or Fortum* or Tazidime*).ti,ab.	8402
33	(Ceftobiprole* or Zevtera*).ti,ab.	262
34	(Ceftolozane* or Tazobactam* or Zerbaxa*).ti,ab.	3883
35	Ceftriaxone/	5711
36	(Ceftriaxone* or Rocephin* or Rocefin*).ti,ab.	9641

#	Searches	Results
37	Cefuroxime/	2190
38	(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab.	4252
39	Chloramphenicol/	20282
40	(Chloramphenicol* or Cloranfenicol* or Kemicetine* or Kloramfenikol*).ti,ab.	26706
41	Ciprofloxacin/	12746
42	(Ciprofloxacin* or Ciproxin*).ti,ab.	23660
43	Clarithromycin/	6010
44	(Clarithromycin* or Clarie* or Klaricid* or Xetinin*).ti,ab.	8472
45	Clindamycin/	5650
46	(Clindamycin* or Dalacin* or Zindaclin*).ti,ab.	9909
47	Amoxicillin-Potassium Clavulanate Combination/	2507
48	(Co-amoxiclav* or Coamoxiclav* or Amox-clav* or Amoxicillin-Clavulanic Acid* or Amoxicillin-Potassium Clavulanate Combination* or Amoxi-Clavulanate* or Clavulanate Potentiated Amoxycillin Potassium* or Clavulanate-Amoxicillin Combination* or Augmentin*).ti,ab.	14740
49	Trimethoprim, Sulfamethoxazole Drug Combination/	6864
50	(Septrin* or Co-trimoxazole* or Cotrimoxazole* or Sulfamethoxazole Trimethoprim Comb* or Trimethoprim Sulfamethoxazole Comb*).ti,ab.	6039
51	Colistin/	3469
52	(Colistin* or Colistimethate* or Colimycin* or Coly-Mycin* or Colymycin* or Colomycin* or Promixin*).ti,ab.	4908
53	Doxycycline/	9252
54	(Doxycycline* or Efracea* or Periostat* or Vibramycin*).ti,ab.	12356
55	(Ertapenem* or Invanz*).ti,ab.	1259
56	Erythromycin/	14235
57	Erythromycin Estolate/	154
58	Erythromycin Ethylsuccinate/	522
59	(Erythromycin* or Erymax* or Tiloryth* or Erythrocin* or Erythrolar* or Erythroped*).ti,ab.	20584
60	Fosfomycin/	1841
61	(Fosfomycin* or Phosphomycin* or Fosfocina* or Monuril* or Monurol* or Fomicyt*).ti,ab.	2633
62	Floxacillin/	739
63	(Floxacillin* or Flucloxacillin*).ti,ab.	841
64	Gentamicins/	18587
65	(Gentamicin* or Gentamycin* or Cidomycin*).ti,ab.	25966
66	Imipenem/	4016
67	(Imipenem* or Primaxin*).ti,ab.	9717
68	Levofloxacin/	2966

#	Searches	Results
69	(Levofloxacin* or Evoxil* or Tavanic*).ti,ab.	6630
70	Linezolid/	2602
71	(Linezolid* or Zyvox*).ti,ab.	4917
72	Meropenem*.ti,ab.	5209
73	(Moxifloxacin* or Avelox*).ti,ab.	4053
74	Ofloxacin/	6226
75	(Ofloxacin* or Tarivid*).ti,ab.	6848
76	Piperacillin/	2715
77	(Piperacillin* or Tazobactam* or Tazocin*).ti,ab.	6833
78	Rifampin/	17369
79	(Rifampicin* or Rifampin* or Rifadin* or Rimactane*).ti,ab.	22712
80	Teicoplanin/	2235
81	(Teicoplanin* or Targocid*).ti,ab.	3469
82	(Telavancin* or Vibativ*).ti,ab.	370
83	(Temocillin* or Negaban*).ti,ab.	303
84	(Tigecycline* or Tygacil*).ti,ab.	2573
85	Vancomycin/	12914
86	(Vancomycin* or Vancomicin* or Vancocin*).ti,ab.	24437
87	or/14-86	276890
88	exp Aminoglycosides/	154192
89	Aminoglycoside*.ti,ab.	18192
90	exp Penicillins/	81362
91	Penicillin*.ti,ab.	54176
92	exp beta-Lactamase inhibitors/	7529
93	((("beta Lactamase*" or betaLactamase*) adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*).ti,ab.	2902
94	beta-Lactams/	6143
95	("beta-Lactam" or betaLactam or "beta Lactam " or "beta-Lactams" or betaLactams or "beta Lactams").ti,ab.	19835
96	exp Carbapenems/	9633
97	Carbapenem*.ti,ab.	10954
98	exp Cephalosporins/	42275
99	Cephalosporin*.ti,ab.	21185
100	exp Fluoroquinolones/	31377
101	Fluoroquinolone*.ti,ab.	14757
102	exp Macrolides/	105899
103	Macrolide*.ti,ab.	14633

#	Searches	Results
104	exp Polymyxins/	8642
105	Polymyxin*.ti,ab.	6754
106	exp Quinolones/	45049
107	Quinolone*.ti,ab.	13128
108	exp Tetracyclines/	47463
109	Tetracycline*.ti,ab.	34151
110	or/88-109	498371
111	Bronchodilator Agents/	19050
112	(Bronchodilator* or broncholytic* or bronchial dilat* or bronchodilating* or bronchodilatant*).ti,ab.	14068
113	analgesics/	46504
114	exp analgesics, non-narcotic/	322909
115	analgesics, short-acting/	8
116	antipyretics/	2593
117	(analgesic* or antipyretic*).ti,ab.	77596
118	Acetaminophen/	17295
119	(paracetamol* or acetaminophen* or Panadol* or perfalgan* or calpol*).ti,ab.	22825
120	Cholinergic antagonists/	4939
121	(Anticholinergic* or "Anti-cholinergic*" or "Anti cholinergic*" or Antimuscarinic* or Anti muscarinic* or Anti-muscarinic*).ti,ab.	14960
122	((("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	23091
123	Adrenergic beta-2 Receptor Agonists/	2590
124	((("adrenergic beta" or "beta adrenergic" or beta2 or "beta 2") adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	23091
125	Albuterol/	9865
126	(Salbutamol* or Albuterol* or Salbulin* or Ventolin* or Salamol*).ti,ab.	9742
127	exp Codeine/	6627
128	(Codeine* or Pholcodine* or Covonia* or Galenphol* or Pavacol* or Galcodine*).ti,ab.	4860
129	Adrenal Cortex Hormones/	63336
130	(Corticosteroid* or corticoid* or Adrenal Cortex Hormone*).ti,ab.	102479
131	Nonprescription Drugs/	5879
132	(non prescription* or nonprescription* or otc or "over the counter*" or "over-the-counter*").ti,ab.	12260
133	Antitussive Agents/	2843
134	Antitussive*.ti,ab.	1887
135	(cough* adj3 (suppressant* or mixture* or syrup* or medicine* or medicinal* or remedy* or remedies* or product or products)).ti,ab.	915

#	Searches	Results
136	exp Histamine Antagonists/	63384
137	Antazoline/	212
138	Brompheniramine/	351
139	Chlorpheniramine/	1989
140	Cinnarizine/	807
141	Cyproheptadine/	2322
142	Diphenhydramine/	4028
143	Doxylamine/	384
144	Ergotamine/	2436
145	Hydroxyzine/	1452
146	Ketotifen/	1176
147	Pizotyline/	283
148	Promethazine/	3131
149	Trimeprazine/	327
150	Tripolidine/	309
151	(histamin* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	9267
152	(antihistamin* or anti-histamin* or Alimemazine* or Trimeprazine* or Antazoline* or Brompheniramine* or Chlorpheniramine* or Chlorphenamine* or Cinnarizine* or Stugeron* or Cyproheptadine* or Periacin* or Diphenhydramine* or Doxylamine* or Ergotamine* or Migril* or Hydroxyzine* or Atarax* or Ketotifen* or Zaditen* or Promethazine* or Phenergan* or Sominex* or Pizotifen* or Pizotyline* or Tripolidine* or Acrivastine*).ti,ab.	28608
153	Demulcents/	4
154	(demulcent* or mucoprotective* or muco protective* or Linctus*).ti,ab.	227
155	Glycerol/	25289
156	(Glycerol* or Glycerine*).ti,ab.	48601
157	Menthol/	1801
158	menthol*.ti,ab.	2459
159	exp Prednisolone/	51035
160	(Prednisolone* or Fluprednisolone* or Methylprednisolone* or Deltacortril* or Dilacort* or Pevanti* or Deltastab* or Predsol*).ti,ab.	38299
161	exp Anti-Inflammatory Agents, Non-Steroidal/	193479
162	nsaid*.ti,ab.	23350
163	((nonsteroid* or non steroid*) adj3 (anti inflammator* or antiinflammator*)).ti,ab.	37267
164	Ibuprofen/	8354
165	(ibuprofen* or arthrofen* or ebufac* or rimafen* or brufen* or calprofen* or feverfen* or nurofen* or orbifen*).ti,ab.	12316
166	Dextromethorphan/	1809

#	Searches	Results
167	Dextromethorphan*.ti,ab.	2510
168	Leukotriene Antagonists/	3063
169	(leukotriene* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*).ti,ab.	3803
170	Montelukast*.ti,ab.	1981
171	(Zafirlukast* or Accolate*).ti,ab.	419
172	exp Expectorants/	16613
173	exp Guaifenesin/	778
174	Ipecac/	639
175	(expectorant* or mucolytic* or guaifenesin* or ipecac* or ipecacuanha*).ti,ab.	3104
176	Mannitol/	12727
177	(Mannitol* or Osmohale* or Bronchitol*).ti,ab.	17701
178	(Dornase alfa* or Dornase alpha* or Pulmozyme*).ti,ab.	241
179	or/111-178	850888
180	Honey/	3401
181	Apitherapy/	115
182	(honey* or lemon*).ti,ab.	22625
183	or/180-182	22957
184	Drugs, Chinese Herbal/	37486
185	Plants, Medicinal/	58550
186	exp Geraniaceae/	607
187	Echinacea/	740
188	Fallopia Japonica/	182
189	Thymus Plant/	1222
190	Eucalyptus/	2153
191	Forsythia/	161
192	exp Glycyrrhiza/	2541
193	Andrographis/	392
194	(herb* or Geraniaceae* or Pelargonium* or Geranium* or Kaloba* or Echinacea* or Coneflower* or Japonica* or Knotweed* or Thyme* or Thymus* or Eucalyptus* or Forsythia* or Forsythiae* or Goldenbell* or Lian Qiao* or Glycyrrhiza* or Licorice* or Liquorice* or Andrographis*).ti,ab.	164328
195	((medicine* or medical* or medicinal* or product or products or remedies* or remedy*) adj3 (plant* or plants or root or roots or flower or flowers or bark or barks or seed or seeds or shrub or shrubs or botanic*).ti,ab.	22887
196	or/184-195	250887
197	Fluid therapy/	19152
198	Drinking/	14161

#	Searches	Results
199	Drinking Behavior/	6832
200	exp Beverages/	124615
201	((water* or fluid* or liquid* or beverage* or drinks) adj3 (consumption* or consume* or consuming* or intake* or drink* or hydrat* or rehydrat* or therap*)).ti,ab.	94064
202	or/197-201	233113
203	watchful waiting/	2814
204	"no intervention".ti,ab.	6973
205	(watchful* adj2 wait*).ti,ab.	2322
206	(wait adj2 see).ti,ab.	1355
207	(active* adj2 surveillance*).ti,ab.	6524
208	(expectant* adj2 manage*).ti,ab.	3052
209	or/203-208	21524
210	Self Care/	31625
211	Self medication/	4619
212	((self or selves or themsel*) adj4 (care or manag*)).ti,ab.	37183
213	or/210-212	59647
214	Inappropriate prescribing/	2123
215	((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab.	29081
216	((prescription* or prescrib*) adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab.	24634
217	((bacter* or antibacter* or anti-bacter* or "anti bacter*" or antimicrobial or anti-microbial or "anti microbial" or antibiot* or anti-biot* or "anti biot*") adj3 ("red flag" or strateg* or appropriat* or inappropriat* or unnecessary or defer* or delay* or no or non or behaviour* or behavior* or optimal or optimi* or reduc* or decreas* or declin* or rate* or improv* or back-up* or backup* or immediate* or rapid* or short* or long* or standby or "stand by" or rescue or escalat* or "de-escalat*" or misuse* or "mis-use*" or overuse* or "over-use*" or "over-prescri*" or abuse*)).ti,ab.	103540
218	or/214-217	154879
219	13 or 87 or 110 or 179 or 183 or 196 or 202 or 209 or 213 or 218	2647827
220	10 and 219	1003
221	Meta-Analysis.pt.	92162
222	Network Meta-Analysis/	224
223	Meta-Analysis as Topic/	17171
224	Review.pt.	2446279
225	exp Review Literature as Topic/	10205

#	Searches	Results
226	(metaanaly* or metanaly* or (meta adj3 analy*)).ti,ab.	131172
227	(review* or overview*).ti.	435849
228	(systematic* adj5 (review* or overview*)).ti,ab.	131188
229	((quantitative* or qualitative*) adj5 (review* or overview*)).ti,ab.	8476
230	((studies or trial*) adj2 (review* or overview*)).ti,ab.	40733
231	(integrat* adj3 (research or review* or literature)).ti,ab.	9924
232	(pool* adj2 (analy* or data)).ti,ab.	25784
233	(handsearch* or (hand adj3 search*)).ti,ab.	8424
234	(manual* adj3 search*).ti,ab.	5301
235	or/221-234	2728598
236	220 and 235	336
237	87 or 110 or 179 or 183 or 196 or 202 or 209 or 213 or 218	2088629
238	10 and 237	785
239	Randomized Controlled Trial.pt.	497753
240	Controlled Clinical Trial.pt.	99278
241	Clinical Trial.pt.	548201
242	exp Clinical Trials as Topic/	332580
243	Placebos/	36441
244	Random Allocation/	99753
245	Double-Blind Method/	157698
246	Single-Blind Method/	26614
247	Cross-Over Studies/	45096
248	((random* or control* or clinical*) adj3 (trial* or stud*)).ti,ab.	1116456
249	(random* adj3 allocat*).ti,ab.	31870
250	placebo*.ti,ab.	209384
251	((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab.	167969
252	(crossover* or (cross adj over*)).ti,ab.	82402
253	or/239-252	1897334
254	238 and 253	223
255	254 not 236	119
256	Observational Studies as Topic/	2837
257	Observational Study/	46904
258	Epidemiologic Studies/	7986
259	exp Case-Control Studies/	950199
260	exp Cohort Studies/	1826884
261	Cross-Sectional Studies/	269973
262	Controlled Before-After Studies/	297

#	Searches	Results
263	Historically Controlled Study/	149
264	Interrupted Time Series Analysis/	376
265	Comparative Study.pt.	1909472
266	case control*.ti,ab.	115049
267	case series.ti,ab.	59627
268	(cohort adj (study or studies)).ti,ab.	156820
269	cohort analy*.ti,ab.	6287
270	(follow up adj (study or studies)).ti,ab.	47177
271	(observational adj (study or studies)).ti,ab.	81749
272	longitudinal.ti,ab.	210768
273	prospective.ti,ab.	509379
274	retrospective.ti,ab.	431941
275	cross sectional.ti,ab.	279020
276	or/256-275	4337949
277	238 and 276	261
278	277 not (236 or 255)	191
279	238 not (236 or 255 or 278)	206

7 Study flow diagram



8 Included studies

8.1 References

Hnin Khin, Nguyen Chau, Carson Kristin V, Evans David J, Greenstone Michael, and Smith Brian J (2015) Prolonged antibiotics for non-cystic fibrosis bronchiectasis in children and adults. The Cochrane database of systematic reviews (8), CD001392

Comments:

Risk of bias assessment using the [CASP Tool](#)

Study reference	Hnin et al. 2015
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	No
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

Barker Alan F, O'Donnell Anne E, Flume Patrick, Thompson Philip J, Ruzi Jonathan D, de Gracia , Javier , Boersma Wim G, De Soyza , Anthony , Shao Lixin, Zhang Jenny, Haas Laura, Lewis Sandra A, Leitzinger Sheila, Montgomery A Bruce, McKevitt Matthew T, Gossage David, Quittner Alexandra L, and O'Riordan Thomas G (2014) Aztreonam for inhalation solution in patients with non-cystic fibrosis bronchiectasis (AIR-BX1 and AIR-BX2): two randomised double-blind, placebo-controlled phase 3 trials. The Lancet. Respiratory medicine 2(9), 738-49

Comments:

Risk of bias assessment using the [CASP Tool](#)

Study reference	Barker et al. 2014
Did the review address a clearly focused question?	Yes
Did the authors look for the right type of papers?	Yes
Do you think all the important, relevant studies were included?	Yes
Did the review's authors do enough to assess the quality of the included studies?	Yes
If the results of the review have been combined, was it reasonable to do so?	N/A
What are the overall results of the review?	See GRADE profiles
How precise are the results?	See GRADE profiles
Can the results be applied to the local population?	Yes
Were all important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

Bilton Diana, Henig Noreen, Morrissey Brian, and Gotfried Mark (2006) Addition of inhaled tobramycin to ciprofloxacin for acute exacerbations of *Pseudomonas aeruginosa* infection in adult bronchiectasis. *Chest* 130(5), 1503-10

Comments:Risk of bias assessment using the [CASP Tool](#)

Study reference	Bilton at al. 2006
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	Yes
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

Comments:

Risk of bias assessment using the [CASP Tool](#)

Study reference	Haworth at al. 2014
Did the trial address a clearly focused issue?	Yes
Was the assignment of patients to treatments randomised?	Yes
Were patients, health workers and study personnel blinded?	Yes
Were the groups similar at the start of the trial?	Yes
Aside from the experimental intervention, were the groups treated equally?	Yes
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes
How large was the treatment effect?	See GRADE profiles
How precise was the estimate of the treatment effect?	See GRADE profiles
Can the results be applied in your context? (or to the local population)	Yes
Were all clinically important outcomes considered?	Yes
Are the benefits worth the harms and costs?	See GRADE profiles

Haworth Charles S, Foweraker Juliet E, Wilkinson Peter, Kenyon Robert F, and Bilton Diana (2014) Inhaled colistin in patients with bronchiectasis and chronic Pseudomonas aeruginosa infection. American journal of respiratory and critical care medicine 189(8), 975-82

9 Studies not prioritised

Study reference	Reason
Brodts Alessandra Monteiro, Stovold Elizabeth, and Zhang Linjie (2014) Inhaled antibiotics for stable non-cystic fibrosis bronchiectasis: a systematic review. The European respiratory journal 44(2), 382-93	More recent systematic review has been prioritised
Fan Li-Chao, Lu Hai-Wen, Wei Ping, Ji Xiao-Bin, Liang Shuo, and Xu Jin-Fu (2015) Effects of long-term use of macrolides in patients with non-cystic fibrosis bronchiectasis: a meta-analysis of randomized controlled trials. BMC infectious diseases 15, 160	More recent systematic review has been prioritised
Gao Yong-Hua, Guan Wei-Jie, Xu Gang, Tang Yan, Gao Yang, Lin Zhi-Ya, Lin Zhi-Min, Zhong Nan-Shan, and Chen Rong-Chang (2014) Macrolide therapy in adults and children with non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. PloS one 9(3), e90047	More recent systematic review has been prioritised
Magis-Escurra Cecile, and Reijers Monique He (2015) Bronchiectasis. BMJ clinical evidence 2015,	Lower quality systematic review
Wu Qibiao, Shen Weixing, Cheng Haibo, and Zhou Xiqiao (2014) Long-term macrolides for non-cystic fibrosis bronchiectasis: a systematic review and meta-analysis. Respirology (Carlton, and Vic.) 19(3), 321-9	More recent systematic review has been prioritised
Wurzel Danielle, Marchant Julie M, Yerkovich Stephanie T, Upham John W, Masters I Brent, and Chang Anne B (2011) Short courses of antibiotics for children and adults with bronchiectasis. The Cochrane database of systematic reviews (6), CD008695	More recent systematic review has been prioritised
Xu L, Zhang F, Du S, Yu Q, Chen L, Long L H, Li Y M, and Jia A H (2016) Inhaled antibiotics in non-cystic fibrosis bronchiectasis: A meta-analysis. Pharmazie 71(9), 491-498	Lower quality systematic review
Yang Jia-Wei, Fan Li-Chao, Lu Hai-Wen, Miao Xia-Yi, Mao Bei, and Xu Jin-Fu (2016) Efficacy and safety of long-term inhaled antibiotic for patients with noncystic fibrosis bronchiectasis: a meta-analysis. The clinical respiratory journal 10(6), 731-739	Lower quality systematic review
Zhuo Guang-Ying, He Qing, Xiang-Lian Li, Ya-Nan Yin, and Si-Te Feng (2014) Prolonged treatment with macrolides in adult patients with non-cystic fibrosis bronchiectasis: meta-analysis of randomized controlled trials. Pulmonary pharmacology & therapeutics 29(1), 80-8	More recent systematic review has been prioritised
Altenburg Josje, de Graaff , Casper S, Stienstra Ymkje, Sloos Jacobus H, van Haren , Eric H J, Koppers Ralph J. H, van der Werf , Tjip S, and Boersma Wim G (2013) Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 309(12), 1251-9	RCT included in a systematic review that has been prioritised
Antoniou S A, and Trofor A C (2011) Inhaled gentamicin in non-cystic fibrosis bronchiectasis: Effects of long-term therapy. Expert Opinion on Pharmacotherapy 12(7), 1191-1194	RCT included in a systematic review that has been prioritised

Study reference	Reason
Chalmers James D, Smith Maeve P, McHugh Brian J, Doherty Cathy, Govan John R, and Hill Adam T (2012) Short- and long-term antibiotic treatment reduces airway and systemic inflammation in non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine 186(7), 657-65	Systematic review has been prioritised
Lourdesamy Anthony, Albert I, and Muthukumar Umadevi (2014) Efficacy of azithromycin in the treatment of bronchiectasis. Respirology (Carlton, and Vic.) 19(8), 1178-82	Systematic review has been prioritised
Masekela R, Anderson R, Gongxeka H, Steel H C, Becker P J, and Green R J (2013) Lack of efficacy of an immunomodulatory macrolide in childhood HIV related bronchiectasis: A randomised, placebo-controlled trial. Journal of Antivirals and Antiretrovirals 5(2), 044-049	Low relevance to current UK practice (children with HIV in South Africa)
Murray Mp, Govan Jr, Doherty Cj, Simpson Aj, Wilkinson Ts, Chalmers Jd, Greening Ap, Haslett C, and Hill At (2011) A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine 183(4), 491-499	RCT included in a systematic review that has been prioritised
Orriols Ramon, Hernando Rosana, Ferrer Adelaida, Terradas Sonia, and Montoro Bruno (2015) Eradication Therapy against <i>Pseudomonas aeruginosa</i> in Non-Cystic Fibrosis Bronchiectasis. Respiration, and international review of thoracic diseases 90(4), 299-305	Systematic review has been prioritised
Rogers Geraint B, Bruce Kenneth D, Martin Megan L, Burr Lucy D, and Serisier David J (2014) The effect of long-term macrolide treatment on respiratory microbiota composition in non-cystic fibrosis bronchiectasis: an analysis from the randomised, double-blind, placebo-controlled BLESS trial. The Lancet. Respiratory medicine 2(12), 988-96	Secondary analysis of a primary RCT that has been prioritised and no additional outcomes of interest
Serisier David J, Bilton Diana, De Soyza , Anthony , Thompson Philip J, Kolbe John, Greville Hugh W, Cipolla David, Bruinenberg Paul, Gonda Igor, and investigators Orbit (2013) Inhaled, dual release liposomal ciprofloxacin in non-cystic fibrosis bronchiectasis (ORBIT-2): a randomised, double-blind, placebo-controlled trial. Thorax 68(9), 812-7	RCT included in a systematic review that has been prioritised
Serisier David J, Martin Megan L, McGuckin Michael A, Lourie Rohan, Chen Alice C, Brain Barbara, Biga Sally, Schlebusch Sanmarie, Dash Peter, and Bowler Simon D (2013) Effect of long-term, low-dose erythromycin on pulmonary exacerbations among patients with non-cystic fibrosis bronchiectasis: the BLESS randomized controlled trial. JAMA 309(12), 1260-7	RCT included in a systematic review that has been prioritised

Study reference	Reason
Valery Patricia C, Morris Peter S, Byrnes Catherine A, Grimwood Keith, Torzillo Paul J, Bauert Paul A, Masters I Brent, Diaz Abbey, McCallum Gabrielle B, Mobberley Charmaine, Tjhung Irene, Hare Kim M, Ware Robert S, and Chang Anne B (2013) Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): a multicentre, double-blind, randomised controlled trial. <i>The Lancet. Respiratory medicine</i> 1(8), 610-20	RCT included in a systematic review that has been prioritised
Wong Conroy, Jayaram Lata, Karalus Noel, Eaton Tam, Tong Cecilia, Hockey Hans, Milne David, Fergusson Wendy, Tuffery Christine, Sexton Paul, Storey Louanne, and Ashton Toni (2012) Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. <i>Lancet (London, and England)</i> 380(9842), 660-7	RCT included in a systematic review that has been prioritised
Yalcin E, Kiper N, Ozcelik U, Dogru D, Firat P, Sahin A, Ariyurek M, Mocan G, Gurcan N, and Gocmen A (2006) Effects of claritromycin on inflammatory parameters and clinical conditions in children with bronchiectasis. <i>Journal of clinical pharmacy and therapeutics</i> 31(1), 49-55	RCT included in a systematic review that has been prioritised

10 Excluded studies

Study reference	Reason for exclusion
Abo-Leyah Hani, and Chalmers James D (2017) New therapies for the prevention and treatment of exacerbations of bronchiectasis. <i>Current opinion in pulmonary medicine</i> 23(3), 218-224	Publication/ study type (not a relevant study)
Aksamit Timothy, Bandel Tiemo-Joerg, Criollo Margarita, De Soyza , Anthony , Elborn J Stuart, Operschall Elisabeth, Polverino Eva, Roth Katrin, Winthrop Kevin L, and Wilson Robert (2017) The RESPIRE trials: Two phase III, randomized, multicentre, placebo-controlled trials of Ciprofloxacin Dry Powder for Inhalation (Ciprofloxacin DPI) in non-cystic fibrosis bronchiectasis. <i>Contemporary clinical trials</i> 58, 78-85	Publication/ study type (abstract only)
Aksamit Tr, Bandel T-J, Criollo M, Elborn J, Lau M, Operschall E, Polverino E, Montegriffo E, Soyza A, Winthrop KI, and Wilson R (2017) Respire 2: ciprofloxacin Dpi 32.5 Mg B.i.d. Administered 14 Days On/off Or 28 Days On/off Vs. Placebo for 48 weeks in patients with non-cystic fibrosis bronchiectasis (NCFB). <i>American journal of respiratory and critical care medicine</i> . Conference: american thoracic society international conference, and ATS 2017. United states 195(no pagination),	Publication/ study type (abstract only)
Albertson T E, Louie S, and Chan A L (2010) The diagnosis and treatment of elderly patients with acute exacerbation of chronic obstructive pulmonary disease and chronic bronchitis. <i>Journal of the American Geriatrics Society</i> 58(3), 570-579	Not relevant population
Albertson Timothy E, Louie Samuel, and Chan Andrew L (2010) The diagnosis and treatment of elderly patients with acute exacerbation of chronic obstructive pulmonary disease and chronic bronchitis. <i>Journal of the American Geriatrics Society</i> 58(3), 570-9	Not relevant population
Altenburg J, Graaff C, Werf T, and Boersma W (2011) Long term azithromycin treatment: a randomised placebo-controlled trial in non-CF bronchiectasis; results from the BAT trial. <i>European respiratory journal</i> 38(no pagination),	Publication/ study type (abstract only)
Altenburg J, Wortel K, van der Werf , T S, and Boersma W G (2015) Non-cystic fibrosis bronchiectasis: clinical presentation, diagnosis and treatment, illustrated by data from a Dutch Teaching Hospital. <i>The Netherlands journal of medicine</i> 73(4), 147-54	Publication/ study type (not a relevant study)
Alves Galvão Márcia G, Rocha Crispino Santos Marilene Augusta, and Alves da Cunha Antonio JI (2016) Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. <i>Cochrane Database of Systematic Reviews</i> (2),	Not relevant population
Amorim A, Gamboa F, and Azevedo P (2013) New advances in the therapy of non-cystic fibrosis bronchiectasis. <i>Revista portuguesa de pneumologia</i> 19(6), 266-75	No relevant outcomes
Andrews J, Sathe N A, Krishnaswami S, and Melissa L (2013) Nonpharmacologic airway clearance techniques in hospitalized patients: A systematic review. <i>Respiratory Care</i> 58(12), 2160-2186	Not relevant intervention

Study reference	Reason for exclusion
Anonymous (2015) Corrections to Long-term azithromycin for Indigenous children with non-cystic-fibrosis bronchiectasis or chronic suppurative lung disease (Bronchiectasis Intervention Study): A multicentre, double-blind, randomised controlled trial [Lancet Respir Med 1, (2013) 610-620]. The Lancet Respiratory Medicine 3(8), e29	Publication/study type (erratum only)
Antonela Antoniu, and Sabina (2012) Inhaled ciprofloxacin for chronic airways infections caused by <i>Pseudomonas aeruginosa</i> . Expert review of anti-infective therapy 10(12), 1439-46	Publication/study type (not a relevant study)
Asintam P, Kiranantawat N, and Juthong S (2012) Can roxithromycin improve quality of life in bronchiectatic patients?. European respiratory journal 40,	Publication/study type (not a relevant study)
Barker A, O'Donnell A, Thompson Pj, Flume P, Ruzi J, Gracia J, Boersma W, Polverino E, Shao L, Zhang J, Leitzinger S, Haas L, McKeivitt M, Montgomery Ab, Quittner A, Gossage D, and O'Riordan T (2013) Two phase 3 placebo-controlled trials of aztreonam lysine for inhalation (AZLI) for non-cystic fibrosis bronchiectasis (NCFB). European respiratory journal 42,	Publication/study type (abstract only)
Bartziokas K, Papadopoulos A, and Kostikas K (2012) The never-ending challenge of chronic cough in adults: A review for the clinician. Pneumon 25(2), 164-175	Publication/study type (not a relevant study)
Bedi P, Chalmers J, Sarvanamuthu P, Rossi A, and Hill A (2016) Atorvastatin as novel treatment in bronchiectasis patients colonized with <i>Pseudomonas aeruginosa</i> . European respiratory journal. Conference: european respiratory society annual congress 2016. United kingdom. Conference start: 20160903. Conference end: 20160907 48(no pagination),	Publication/study type (abstract only)
Bennoor Ks, Afreen Kf, Hossain Ma, Mahmud Am, and Hassan Mr (2012) Inhaled mannitol in patients with bronchiectasis: effect on lung function and health status. Respirology. 17, 49	Publication/study type (abstract only)
Bilton D, Daviskas E, Jaques A, Anderson S, and Charlton B (2008) A randomised placebo-controlled trial of inhaled mannitol in patients with bronchiectasis. European respiratory society annual congress, berlin, germany, and october 4-8 , [P602]	Publication/study type (abstract only)
Bilton D, Loebinger M R, and Wilson R (2014) Non-cystic fibrosis bronchiectasis: An evidence-base for new therapies. The Lancet Respiratory Medicine 2(12), 958-960	Publication/study type (not a relevant study)
Bilton D, Serisier Dj, Soyza At, Wolfe R, and Bruinenberg P (2011) Multicenter, randomized, double-blind, placebocontrolled study (ORBIT 1) to evaluate the efficacy, safety, and tolerability of once daily ciprofloxacin for inhalation in the management of <i>Pseudomonas aeruginosa</i> infections in patients with non-cystic fibrosis bronchiectasis. European respiratory journal 38(no pagination),	Publication/study type (abstract only)

Study reference	Reason for exclusion
Bilton Diana, Daviskas Evangelia, Anderson Sandra D, Kolbe John, King Gregory, Stirling Rob G, Thompson Bruce R, Milne David, Charlton Brett, and Investigators B (2013) Phase 3 randomized study of the efficacy and safety of inhaled dry powder mannitol for the symptomatic treatment of non-cystic fibrosis bronchiectasis. Chest 144(1), 215-25	Excluded after consultation (non-antimicrobial/prevention)
Bilton Diana, Tino Gregory, Barker Alan F, Chambers Daniel C, De Soyza , Anthony , Dupont Lieven J. A, O'Dochartaigh Conor, van Haren , Eric H J, Vidal Luis Otero, Welte Tobias, Fox Howard G, Wu Jian, Charlton Brett, and Investigators B Study (2014) Inhaled mannitol for non-cystic fibrosis bronchiectasis: a randomised, controlled trial. Thorax 69(12), 1073-9	Excluded after consultation (non-antimicrobial/prevention)
Bilton D, Tino G, Barker A, Chambers D, Soyza A, and Dupont L (2013) Inhaled mannitol for non-cystic fibrosis bronchiectasis - results of a 12 month, multi-centre, double-blind, controlled study. European respiratory society annual congress, 2013 sept 7-11, barcelona, and spain 42(Suppl 57), 140s [P746]	Publication/study type (abstract only)
Bilton Diana (2008) Update on non-cystic fibrosis bronchiectasis. Current opinion in pulmonary medicine 14(6), 595-9	Publication/study type (not relevant study)
Blasi Francesco, Page Clive, Rossolini Gian Maria, Pallecchi Lucia, Matera Maria Gabriella, Rogliani Paola, and Cazzola Mario (2016) The effect of N-acetylcysteine on biofilms: Implications for the treatment of respiratory tract infections. Respiratory medicine 117, 190-7	Publication/study type (not an RCT)
Boersma W, Altenburg J, and Werf T (2012) Evaluation of symptoms score and qol in azithromycin maintenance treatment: results of a rct trial in patients with bronchiectasis. American journal of respiratory and critical care medicine 185,	Publication/study type (abstract only)
Boren Eric J, Teuber Suzanne S, and Gershwin M Eric (2008) A review of non-cystic fibrosis pediatric bronchiectasis. Clinical reviews in allergy & immunology 34(2), 260-73	Publication/study type (not a relevant study)
Bradley Judy, Lavery Katherine, Rendall Jackie, and Elborn J Stuart (2006) Managing bronchiectasis. The Practitioner 250(1681), 194-passim	Publication/study type (not a relevant study)
Burr L, Rogers G, Taylor S, McGuckin M, and Serisier D (2015) Sub inhibitory erythromycin reduces the expression of key p. aeruginosa virulence determinants in non-CF bronchiectasis subjects. Respirology (carlton, and vic.) 20(Suppl 2), 29 [to 043]	Publication/study type (abstract only)
Burr Lucy D, Rogers Geraint B, Chen Alice C. H, Hamilton Brett R, Pool Gertruida F, Taylor Steven L, Venter Deon, Bowler Simon D, Biga Sally, and McGuckin Michael A (2016) Macrolide Treatment Inhibits <i>Pseudomonas aeruginosa</i> Quorum Sensing in Non-Cystic Fibrosis Bronchiectasis. An Analysis from the Bronchiectasis and Low-Dose Erythromycin Study Trial. Annals of the American Thoracic Society 13(10), 1697-1703	Publication/study type

Study reference	Reason for exclusion
Byrnes C (2006) Non cystic fibrosis bronchiectasis. Paediatric Respiratory Reviews 7(SUPPL. 1), S255-S257	Publication/study type (not relevant study type)
Byrnes Cass (2006) Non cystic fibrosis bronchiectasis. Paediatric respiratory reviews 7 Suppl 1, S255-7	Publication/study type (not relevant study type)
Cartlidge Manjit K, and Hill Adam T (2017) Inhaled or nebulised ciprofloxacin for the maintenance treatment of bronchiectasis. Expert opinion on investigational drugs 26(9), 1091-1097	No relevant outcomes
Chalmers James D, Aliberti Stefano, and Blasi Francesco (2015) Management of bronchiectasis in adults. The European respiratory journal 45(5), 1446-62	Publication/study type (not relevant study type)
Chalmers James D, and Sethi Sanjay (2017) Raising awareness of bronchiectasis in primary care: overview of diagnosis and management strategies in adults. NPJ primary care respiratory medicine 27(1), 18	Publication/study type (not relevant study type)
Chandra Ar, Jones As, and King Gg (2008) Effects of inhaled mannitol treatment on airway wall dimensions measured by HRCT in patients with bronchiectasis. American thoracic society international conference, may 16-21, 2008, and toronto , Poster #121	Publication/study type (abstract only)
Chang A B, Oppenheimer J J, Weinberger M, Rubin B K, and Irwin R S (2016) Children with chronic wet or productive cough--Treatment and investigations. Chest 149(1), 120-142	Not relevant population
Chang A B, Peake J, and McElrea M S (2008) Anti-histamines for prolonged non-specific cough in children. The Cochrane database of systematic reviews (2), CD005604	Not relevant population
Chang A B, Redding G J, and Everard M L (2008) Chronic wet cough: Protracted bronchitis, chronic suppurative lung disease and bronchiectasis. Pediatric pulmonology 43(6), 519-31	Publication/study type (not relevant study type)
Chang Anne B, Grimwood Keith, Maguire Graeme, King Paul T, Morris Peter S, and Torzillo Paul J (2008) Management of bronchiectasis and chronic suppurative lung disease in indigenous children and adults from rural and remote Australian communities. The Medical journal of Australia 189(7), 386-93	No relevant outcomes
Chang Anne B, Marsh Robyn L, Smith-Vaughan Heidi C, and Hoffman Lucas R (2012) Emerging drugs for bronchiectasis. Expert opinion on emerging drugs 17(3), 361-78	Publication/study type (not relevant study type)
Chang Anne B, Oppenheimer John J, Weinberger Miles, Rubin Bruce K, and Irwin Richard S (2016) Children With Chronic Wet or Productive Cough--Treatment and Investigations: A Systematic Review. Chest 149(1), 120-42	Not relevant population
Cramer Cassondra L, Patterson Allie, Alchakaki Abdulrazak, and Soubani Ayman O (2017) Immunomodulatory indications of azithromycin in respiratory disease: a concise review for the clinician. Postgraduate medicine 129(5), 493-499	Publication/study type (not relevant study type)

Study reference	Reason for exclusion
Crosbie P A. J, and Woodhead M A (2009) Long-term macrolide therapy in chronic inflammatory airway diseases. The European respiratory journal 33(1), 171-81	Publication/ study type (not relevant study type)
Dal Negro, R W, Micheletto C, and Tognella S (2011) Use of aerosols in bronchiectasis patients. Monaldi archives for chest disease = Archivio Monaldi per le malattie del torace 75(3), 185-93	Publication/ study type (not relevant study type)
Daviskas E, Bilton D, Jaques A, Anderson S, and Charlton B (2009) A randomised, placebo -controlled trial of inhaled mannitol in patients with bronchiectasis. Respirology (carlton, and vic.) 14(Suppl 1), A29	Publication/ study type (abstract only)
Daviskas Evangelia, and Anderson Sandra D (2006) Hyperosmolar agents and clearance of mucus in the diseased airway. Journal of aerosol medicine : the official journal of the International Society for Aerosols in Medicine 19(1), 100-9	No relevant outcomes
Daviskas Evangelia, and Rubin Bruce K (2013) Effect of inhaled dry powder mannitol on mucus and its clearance. Expert review of respiratory medicine 7(1), 65-75	No relevant outcomes
Daviskas Evangelia, Anderson Sandra D, and Young Iven H (2010) Effect of mannitol and repetitive coughing on the sputum properties in bronchiectasis. Respiratory medicine 104(3), 371-7	No relevant outcomes
Dimakou K, Liapikou A, Triantafilidou C, Chrysikos S, Kaponi M, Melachroinou M, Gousiou A, and Toumbis M (2017) Non cf bronchiectasis: the effect of inhaled antibiotics (tobramycin and colistin) in patients with <i>Pseudomonas aeruginosa</i> in sputum. American journal of respiratory and critical care medicine. Conference: american thoracic society international conference, and ATS 2017. United states 195(no pagination),	Publication/ study type (abstract only)
Dimakou K, Triantafillidou C, Tsikritsaki K, Gousiou A, Dervas A, and Toumbis M (2014) Non CF bronchiectasis: the effect of inhaled antibiotics (tobramycin and colistin) in patients with <i>Pseudomonas aeruginosa</i> . European respiratory journal 44,	Publication/ study type (abstract only)
Ding H, Wang J-G, Sun X-Y, and Xu L-J (2006) Responsibility to bronchodilator and glucocorticosteroid in patients with bronchiectasia and reversible airflow limitation. Journal of jilin university medicine edition 32(5), 872-875	Publication/ study type (unable to source full paper)
Donovan T, Felix L M, Chalmers J D, Milan S J, Mathioudakis A G, and Spencer S (2017) Continuous versus intermittent antibiotics for non-cystic fibrosis bronchiectasis. Cochrane Database of Systematic Reviews 2017(7), 1-13	Publication/ study type (not relevant study type)
Dryden Matthew (2017) Reactive oxygen therapy: a novel antimicrobial. International journal of antimicrobial agents ,	Publication/ study type (not relevant study type)
ElMaraachli Wael, Conrad Douglas J, and Wang Angela C. C (2016) Using Cystic Fibrosis Therapies for Non-Cystic Fibrosis Bronchiectasis. Clinics in chest medicine 37(1), 139-46	Publication/ study type (not relevant study type)

Study reference	Reason for exclusion
Evans D J, Bara A I, and Greenstone M (2007) Prolonged antibiotics for purulent bronchiectasis in children and adults. The Cochrane database of systematic reviews (2), CD001392	Publication/ study type (updated version available)
Falagas Matthew E, Trigkidis Kyriakos K, and Vardakas Konstantinos Z (2015) Inhaled antibiotics beyond aminoglycosides, polymyxins and aztreonam: A systematic review. International journal of antimicrobial agents 45(3), 221-33	Publication/ study type (not relevant study type)
Feldman Charles (2011) Bronchiectasis: new approaches to diagnosis and management. Clinics in chest medicine 32(3), 535-46	Publication/ study type (not relevant study type)
Feldman Charles (2012) The use of antiinflammatory therapy and macrolides in bronchiectasis. Clinics in chest medicine 33(2), 371-80	Publication/ study type (not relevant study type)
Felix L M, Grundy S, Milan S J, Armstrong R, Harrison H, Lynes D, and Spencer S (2017) Dual antibiotics for non-cystic fibrosis bronchiectasis. Cochrane Database of Systematic Reviews 2017(1), CD012514	Publication/ study type (not relevant study type)
Figueiredo Bruna de Campos Guimaraes E, and Ibiapina Cassio da Cunha (2011) The role of macrolides in noncystic fibrosis bronchiectasis. Pulmonary medicine 2011, 751982	Publication/ study type (not relevant study type)
Fjaellegaard Katrine, Sin Melda Donmez, Browatzki Andrea, and Ulrik Charlotte Suppli (2017) Antibiotic therapy for stable non-CF bronchiectasis in adults - A systematic review. Chronic respiratory disease 14(2), 174-186	Publication/ study type (not relevant study type)
Flight W G, and Jones A M (2012) Cystic fibrosis, primary ciliary dyskinesia and non-cystic fibrosis bronchiectasis: Update 2008-11. Thorax 67(7), 645-649	Publication/ study type (not relevant study type)
Flume Patrick A, and VanDevanter Donald R (2015) Clinical applications of pulmonary delivery of antibiotics. Advanced drug delivery reviews 85, 1-6	Publication/ study type (not relevant study type)
Gardiner Samantha J, Chang Anne B, Marchant Julie M, and Petsky Helen L (2016) Codeine versus placebo for chronic cough in children. The Cochrane database of systematic reviews 7, CD011914	Publication/ study type (no data reported)
Garrod R, and Lasserson T (2007) Role of physiotherapy in the management of chronic lung diseases: An overview of systematic reviews. Respiratory Medicine 101(12), 2429-2436	No relevant outcomes
Gjoerup Juliana, Hilberg Ole, and Bendstrup Elisabeth (2012) Inhaled mannitol in the treatment of non-cystic fibrosis bronchiectasis in adults. Respirology (Carlton, and Vic.) 17(6), 927-32	Publication/ study type (not relevant study type)

Study reference	Reason for exclusion
Goeminne Pieter, and Dupont Lieven (2010) Non-cystic fibrosis bronchiectasis: diagnosis and management in 21st century. Postgraduate medical journal 86(1018), 493-501	Publication/study type (not relevant study type)
Goldman N, Loebinger M R, and Wilson R (2016) Long-term antibiotic treatment for non-cystic fibrosis bronchiectasis in adults: evidence, current practice and future use. Expert Review of Respiratory Medicine 10(12), 1259-1268	Publication/study type (not relevant study type)
Goyal Vikas, and Chang Anne B (2014) Combination inhaled corticosteroids and long-acting beta2-agonists for children and adults with bronchiectasis. The Cochrane database of systematic reviews (6), CD010327	Excluded after consultation (non-antimicrobial/prevention)
Goyal V, and Chang A B (2014) Combination inhaled corticosteroids and long-acting beta2-agonists for children and adults with bronchiectasis. Cochrane Database of Systematic Reviews 2017(8), CD010327	Publication/study type (duplicate)
Goyal Vikas, Grimwood Keith, Marchant Julie, Masters I Brent, and Chang Anne B (2016) Pediatric bronchiectasis: No longer an orphan disease. Pediatric pulmonology 51(5), 450-69	Publication/study type (not relevant study type)
Grimwood Keith, Bell Scott C, and Chang Anne B (2014) Antimicrobial treatment of non-cystic fibrosis bronchiectasis. Expert review of anti-infective therapy 12(10), 1277-96	Publication/study type (not relevant study type)
Guan Wei-Jie, Gao Yong-Hua, Xu Gang, Li Hui-Min, Yuan Jing-Jing, Zheng Jin-Ping, Chen Rong-Chang, and Zhong Nan-Shan (2016) Bronchodilator response in adults with bronchiectasis: correlation with clinical parameters and prognostic implications. Journal of thoracic disease 8(1), 14-23	Publication/study type (not relevant study type)
Guimaraes Fernando S, Moco Vanessa J. R, Menezes Sara L. S, Dias Cristina M, Salles Raquel E. B, and Lopes Agnaldo J (2012) Effects of ELTGOL and Flutter VPR1 on the dynamic and static pulmonary volumes and on the secretion clearance of patients with bronchiectasis. Revista brasileira de fisioterapia (Sao Carlos (Sao Paulo, and Brazil)) 16(2), 108-13	Not relevant intervention
Hagerman Jennifer K, Hancock Kim E, and Klepser Michael E (2006) Aerosolised antibiotics: a critical appraisal of their use. Expert opinion on drug delivery 3(1), 71-86	Publication/study type (not relevant study type)
Hampel B, Schoeman O, Reimnitz P, Jones P, and Wilson R (2011) Health status impact of ciprofloxacin dry powder for inhalation in patients with non-cystic fibrosis bronchiectasis. European respiratory journal 38(no pagination),	No relevant outcomes
Hart Anna, Sugumar Karnam, Milan Stephen J, Fowler Stephen J, and Crossingham Iain (2014) Inhaled hyperosmolar agents for bronchiectasis. The Cochrane database of systematic reviews (5), CD002996	Excluded after consultation (non-antimicrobial/prevention)

Study reference	Reason for exclusion
Haworth C, Bilton D, and Kenyon R (2013) Nebulised colistimethate sodium improves quality of life in patients with bronchiectasis colonised by <i>Pseudomonas aeruginosa</i> . European respiratory journal 42,	Publication/ study type (abstract only)
Haworth C, Foweraker J, Wilkinson P, Kenyon R, and Bilton D (2013) Multicenter randomized double blind placebo controlled trial of promixin (colistin) delivered through the I-neb in patients with non-CF bronchiectasis and chronic <i>Pseudomonas aeruginosa</i> infection. American journal of respiratory and critical care medicine 187,	Publication/ study type (abstract only)
Haworth C, Wanner A, Froehlich J, O'Neal T, Davis A, Gonda I, and O'Donnell A (2017) Inhaled liposomal ciprofloxacin in patients with bronchiectasis and chronic <i>Pseudomonas aeruginosa</i> infection: results from two parallel phase iii trials (Orbit-3 and -4). American journal of respiratory and critical care medicine. Conference: american thoracic society international conference, and ATS 2017. United states 195(no pagination),	Publication/ study type (abstract only)
Haworth Charles S, Bilton Diana, and Elborn J Stuart (2014) Long-term macrolide maintenance therapy in non-CF bronchiectasis: evidence and questions. Respiratory medicine 108(10), 1397-408	Publication/ study type (not relevant study type)
Hernando Rosana, Drobnic Maria Estrella, Cruz Maria Jesus, Ferrer Adelaida, Sune Pilar, Montoro J Bruno, and Orriols Ramon (2012) Budesonide efficacy and safety in patients with bronchiectasis not due to cystic fibrosis. International journal of clinical pharmacy 34(4), 644-50	Excluded after consultation (non- antimicrobial/ prevention)
Hester Klm, Newton J, Rapley T, and Soyza A (2016) Evaluation of a novel intervention for patients with bronchiectasis: the bronchiectasis information and education feasibility (BRIEF) study. Thorax. Conference: british thoracic society winter meeting 2016. United kingdom 71, A265-a266	Publication/ study type (abstract only)
Hill Adam T (2016) Macrolides for Clinically Significant Bronchiectasis in Adults: Who Should Receive This Treatment?. Chest 150(6), 1187-1193	Publication/ study type (not relevant study type)
Hossain A, Ahamed M, and Sharkar Zh (2010) Change in clinical outcome of exacerbation of bronchiectasis on addition of nebulized gentamicin to systemic antibiotic. Congress of the asian pacific society of respirology, manila, and philippines ,	Publication/ study type (abstract only)
Huang H, Zhang Y, Yang P, Xue J, Tang J, and Guyatt G (2014) The pilot study of traditional chinese medicine in the treatment of stable bronchiectasis by N-of-1 trials. Journal of alternative and complementary medicine (new york, and N.Y.) 20(5), A39	Publication/ study type (not relevant study type)
Huang Haiyin, Yang Peilan, Xue Jingjing, Tang Jie, Ding Liyu, Ma Ying, Wang Jie, Guyatt Gordon H, Vanniyasingam Thuva, and Zhang Yuqing (2014) Evaluating the Individualized Treatment of Traditional Chinese Medicine: A Pilot Study of N-of-1 Trials. Evidence-based complementary and alternative medicine : eCAM 2014, 148730	Not relevant intervention

Study reference	Reason for exclusion
Ilowite Jonathan, Spiegler Peter, and Chawla Shaline (2008) Bronchiectasis: new findings in the pathogenesis and treatment of this disease. Current opinion in infectious diseases 21(2), 163-7	Publication/ study type (not relevant study type)
Ilowite Jonathan, Spiegler Peter, and Kessler Heather (2009) Pharmacological treatment options for bronchiectasis: focus on antimicrobial and anti-inflammatory agents. Drugs 69(4), 407-19	Publication/ study type (not relevant study type)
Jayaram L, Wong Ca, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Ferguson W, Tuffery C, Sexton P, Storey L, and Ashton T (2012) Azithromycin decreases exacerbations in noncystic fibrosis bronchiectasis. Respirology. 17(Suppl 1), 35	Publication/ study type (abstract only)
Jelic S, Cunningham J A, and Factor P (2008) Clinical review: Airway hygiene in the intensive care unit. Critical Care 12(2), 209	Not relevant population
Juthong S, and Eiamsa-ard S (2011) The effects of roxithromycin as anti-inflammatory agent on clinical outcomes in patient with bronchiectasis: a double blinded randomized controlled study. European respiratory journal 38(no pagination),	Publication/ study type (abstract only)
Kapur N, and Chang A B (2007) Oral non steroid anti-inflammatories for children and adults with bronchiectasis. Cochrane Database of Systematic Reviews (4), CD006427	Publication/ study type (no data reported)
Kapur N, and Chang A B (2007) Oral non steroid anti-inflammatories for children and adults with bronchiectasis. The Cochrane database of systematic reviews (4), CD006427	No relevant outcomes
Kapur Nitin, Bell Scott, Kolbe John, and Chang Anne B (2009) Inhaled steroids for bronchiectasis. The Cochrane database of systematic reviews (1), CD000996	Excluded after consultation (non- antimicrobial/ prevention)
Kapur N, Bell S, Kolbe J, and Chang A B (2009) Inhaled steroids for bronchiectasis. Cochrane Database of Systematic Reviews (1), CD000996	Publication/ study type (duplicate)
Kellett Fiona, and Robert Niven M (2011) Nebulised 7% hypertonic saline improves lung function and quality of life in bronchiectasis. Respiratory medicine 105(12), 1831-5	
Kelly H W (2010) Mucolytic therapy: What, when, where, why, and what is the evidence?. Pediatric, Allergy, Immunology, and and Pulmonology 23(2), 151-154	Publication/ study type (not relevant study type)
Kim Daniel N, and Lazarus Angeline A (2008) Management of bronchiectasis. Disease-a-month : DM 54(8), 540-6	Publication/ study type (not relevant study type)
Kim S W, Kuti J L, and Nicolau D P (2008) Inhaled antimicrobial therapies for respiratory infections. Current Infectious Disease Reports 10(1), 29-36	Publication/ study type (not relevant study type)

Study reference	Reason for exclusion
King Paul T, and Holmes Peter W (2012) Use of antibiotics in bronchiectasis. Reviews on recent clinical trials 7(1), 24-30	Publication/study type (not relevant study type)
Lavery K, O'Neill B, Elborn S, and Bradley J (2007) Self-management in bronchiectasis. An exploratory randomised controlled trial of a disease specific expert patient programme compared to usual care in patients with bronchiectasis. Thorax 62(Suppl iii), A18	Publication/study type (abstract only)
Lavery Katherine A, O'Neill Brenda, Parker Michael, Elborn J Stuart, and Bradley Judy M (2011) Expert patient self-management program versus usual care in bronchiectasis: a randomized controlled trial. Archives of physical medicine and rehabilitation 92(8), 1194-201	Not relevant intervention
Lee Annemarie L, Burge Angela T, and Holland Anne E (2015) Airway clearance techniques for bronchiectasis. The Cochrane database of systematic reviews (11), CD008351	Not relevant intervention
Li M, Jiang D, Yu S, and Wang Y (2015) Comments on Zhuo et al.: Prolonged treatment with macrolides in adult patients with non-cystic fibrosis bronchiectasis: Meta-analysis of randomized controlled trials. Pulmonary Pharmacology and Therapeutics 30, 93-95	Publication/study type (not relevant study type)
Liapikou Adamantia, and Torres Antoni (2014) Pharmacotherapy for lower respiratory tract infections. Expert opinion on pharmacotherapy 15(16), 2307-18	Publication/study type (not relevant study type)
Liu Jf, Zhong Xn, He Zy, Zhong Dj, Bai J, Zhang Jq, and Zhong W (2012) Impact of treatment with low dose roxithromycin on stable bronchiectasis. Zhonghua jie he he hu xi za zhi [Chinese journal of tuberculosis and respiratory diseases] 35(11), 824-827	Publication/study type (abstract only)
Loebinger Michael R, and Wilson Robert (2007) Pharmacotherapy for bronchiectasis. Expert opinion on pharmacotherapy 8(18), 3183-93	Publication/study type (not relevant study type)
Mackley R (2013) Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis. Thorax 68(9), 866	Publication/study type (abstract only)
Mandal P, and Hill A T (2013) Bronchiectasis: Breaking the cycle of inflammation and infection. The Lancet Respiratory Medicine 1(1), e5-e6	Publication/study type (unable to source full paper)
Martinez-Garcia Miguel A, Perpina-Tordera Miguel, Roman-Sanchez Pilar, and Soler-Cataluna Juan Jose (2006) Inhaled steroids improve quality of life in patients with steady-state bronchiectasis. Respiratory medicine 100(9), 1623-32	Excluded after consultation (non-antimicrobial/prevention)

Study reference	Reason for exclusion
Martinez-Garcia Miguel Angel, Soler-Cataluna Juan J, Catalan-Serra Pablo, Roman-Sanchez Pilar, and Tordera Miguel Perpina (2012) Clinical efficacy and safety of budesonide-formoterol in non-cystic fibrosis bronchiectasis. Chest 141(2), 461-468	Excluded after consultation (non-antimicrobial/prevention)
Masekela R, and Green R J (2012) The role of macrolides in childhood non-cystic fibrosis-related bronchiectasis. Mediators of inflammation 2012, 134605	Publication/study type (not relevant study type)
Maselli Diego J, Amalakuhan Bravein, Keyt Holly, and Diaz Alejandro A (2017) Suspecting non-cystic fibrosis bronchiectasis: What the busy primary care clinician needs to know. International journal of clinical practice 71(2),	Publication/study type (not relevant study type)
Maselli Diego J, Keyt Holly, and Restrepo Marcos I (2017) Inhaled Antibiotic Therapy in Chronic Respiratory Diseases. International journal of molecular sciences 18(5),	Publication/study type (not relevant study type)
McCullough Amanda, Thomas Elizabeth T, Ryan Cristin, Bradley Judy M, O'Neill Brenda, Elborn Stuart, and Hughes Carmel (2015) Interventions for enhancing adherence to treatment in adults with bronchiectasis. The Cochrane database of systematic reviews (11), CD011023	Publication/study type (not relevant study type)
McCullough Ar, Ryan C, O'Neill B, Elborn Js, Bradley Jm, and Hughes Cm (2014) Interventions for enhancing adherence to treatment in adults with chronic respiratory disease: a systematic review. American journal of respiratory and critical care medicine 189,	Publication/study type (abstract only)
McDonnell M J, Ward C, Lordan J L, and Rutherford R M (2013) Non-cystic fibrosis bronchiectasis. QJM : monthly journal of the Association of Physicians 106(8), 709-15	Publication/study type (not relevant study type)
McNeill S (2014) Erythromycin to prevent exacerbations of bronchiectasis. Thorax 69(2), 186	Publication/study type (abstract only)
McShane Pamela J, Naureckas Edward T, Tino Gregory, and Strek Mary E (2013) Non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine 188(6), 647-56	Publication/study type (not relevant study type)
Metersky Mark L (2010) New treatment options for bronchiectasis. Therapeutic advances in respiratory disease 4(2), 93-9	Publication/study type (not relevant study type)
Murray Maeve P, Govan John R. W, Doherty Catherine J, Simpson A John, Wilkinson Thomas S, Chalmers James D, Greening Andrew P, Haslett Christopher, and Hill Adam T (2011) A randomized controlled trial of nebulized gentamicin in non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine 183(4), 491-9	Publication/study type (duplicate)

Study reference	Reason for exclusion
Murray Mp, Govan Rw, Doherty Cj, Greening Ap, Gray Rd, and Simpson Aj (2009) Long-term nebulised gentamicin in non-cystic fibrosis bronchiectasis improves microbial load, exercise tolerance, exacerbation frequency and health-related quality of life. Thorax 64(Suppl IV), A63 [s125]	Publication/ study type (abstract only)
Nair Girish B, and Ilowite Jonathan S (2012) Pharmacologic agents for mucus clearance in bronchiectasis. Clinics in chest medicine 33(2), 363-70	Publication/ study type (not relevant study type)
Nathan Anna Marie, de Bruyne , Jessie Anne, Eg Kah Peng, and Thavagnanam Surendran (2017) Review: Quality of Life in Children with Non-cystic Fibrosis Bronchiectasis. Frontiers in pediatrics 5, 84	Publication/ study type (not relevant study type)
Nct (2008) Inhaled Mannitol as a Mucoactive Therapy for Bronchiectasis. Http://clinicaltrials.gov/show/nct00669331 ,	Publication/ study type (unpublished study)
O'Donnell A, Bilton D, Serisier D, Wanner A, Froehlich J, Bruinenberg P, and Gonda I (2016) A phase 3 study design of Pulmaquin in non-cystic fibrosis bronchiectasis (NCFBE) patients chronically colonized with <i>Pseudomonas aeruginosa</i> (PA). Pneumologie. Conference: 1st world bronchiectasis conference. Germany. Conference start: 20160707. Conference end: 20160709 70(10) (no pagination),	Publication/ study type (unable to source full paper)
O'Donnell Anne E (2012) Antimicrobial therapy for bronchiectasis. Clinics in chest medicine 33(2), 381-6	Publication/ study type (not relevant study type)
O'Donnell Anne E (2015) Bronchiectasis: which antibiotics to use and when?. Current opinion in pulmonary medicine 21(3), 272-7	Publication/ study type (not relevant study type)
O'Grady Kerry-Ann F, and Grimwood Keith (2017) The Likelihood of Preventing Respiratory Exacerbations in Children and Adolescents with either Chronic Suppurative Lung Disease or Bronchiectasis. Frontiers in pediatrics 5, 58	Publication/ study type (not relevant study type)
Panyarath P, and Juthong S (2016) Efficacy of roflumilast on exacerbations in patients with non-cystic fibrosis bronchiectasis: a preliminary randomized double-blind placebo-controlled trial. Respirology. Conference: 21st congress of the asian pacific society of respirology, and APSR 2016. Thailand. Conference start: 20161112. Conference end: 20161115 21, 126	Publication/ study type (abstract only)
Pappalettera Maria, Aliberti Stefano, Castellotti Paola, Ruvolo Leonardo, Giunta Valeria, and Blasi Francesco (2009) Bronchiectasis: an update. The clinical respiratory journal 3(3), 126-34	Publication/ study type (not relevant study type)
Patterson J E, Hewitt O, Kent L, Bradbury I, Elborn J S, and Bradley J M (2007) Acapella versus 'usual airway clearance' during acute exacerbation in bronchiectasis: A randomized crossover trial. Chronic Respiratory Disease 4(2), 67-74	Not relevant intervention

Study reference	Reason for exclusion
Pizzutto Susan J, Upham John W, Yerkovich Stephanie T, and Chang Anne B (2016) Inhaled non-steroid anti-inflammatories for children and adults with bronchiectasis. The Cochrane database of systematic reviews (1), CD007525	Not relevant population
Prakash B (2013) Is azithromycin the answer to all flare-ups?. Clinical Pulmonary Medicine 20(3), 158	Publication/study type (not relevant study type)
Quittner A, Soyza A, Aksamit Tr, Bandel T-J, Criollo M, Elborn J, Filonenko A, Krahn U, Lau M, Operschall E, Polverino E, Roth K, Winthrop KI, and Wilson R (2017) Effects of ciprofloxacin dry powder for inhalation (ciprofloxacin DPI) on health-related quality of life in patients with non-cystic fibrosis bronchiectasis (NCFB): results from the phase iii respire 1 study. American journal of respiratory and critical care medicine. Conference: american thoracic society international conference, and ATS 2017. United states 195(no pagination),	Publication/study type (abstract only)
Rademacher Jessica, and Welte Tobias (2011) Bronchiectasis--diagnosis and treatment. Deutsches Arzteblatt international 108(48), 809-15	Publication/study type (not relevant study type)
Redding Gregory J (2009) Bronchiectasis in children. Pediatric clinics of North America 56(1), 157-xi	Publication/study type (not relevant study type)
Rempe S, Hayden J M, Robbins R A, and Hoyt J C (2007) Tetracyclines and pulmonary inflammation. Endocrine, and metabolic & immune disorders drug targets 7(4), 232-6	Publication/study type (not relevant study type)
Restrepo Marcos I, Keyt Holly, and Reyes Luis F (2015) Aerosolized Antibiotics. Respiratory care 60(6), 762-3	Publication/study type (not relevant study type)
Restrepo Ruben D (2007) Inhaled adrenergics and anticholinergics in obstructive lung disease: do they enhance mucociliary clearance?. Respiratory care 52(9), 1159-5	Not relevant population
Rogers G B, Zain N M. M, Bruce K D, Burr L D, Chen A C, Rivett D W, McGuckin M A, and Serisier D J (2014) A novel microbiota stratification system predicts future exacerbations in bronchiectasis. Annals of the American Thoracic Society 11(4), 496-503	Publication/study type (not relevant study type)
Rosen Mark J (2006) Chronic cough due to bronchiectasis: ACCP evidence-based clinical practice guidelines. Chest 129(1 Suppl), 122S-131S	Publication/study type (not relevant study type)
Rubin Bruce K (2008) Aerosolized antibiotics for non-cystic fibrosis bronchiectasis. Journal of aerosol medicine and pulmonary drug delivery 21(1), 71-6	Publication/study type (not relevant study type)

Study reference	Reason for exclusion
Sadigov As, and Mammadov Gt (2013) Azythromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis: how we can improve the clinical features of severe disease?. American journal of respiratory and critical care medicine 187,	Publication/ study type (abstract only)
Serisier D J, and Martin M L (2011) Long-term, low-dose erythromycin in bronchiectasis subjects with frequent infective exacerbations. Respiratory medicine 105(6), 946-9	Publication/ study type (not relevant study type)
Serisier Dj, Bowler Sd, McGuckin M, Chen A, Lourie R, and Martin MI (2012) The bronchiectasis and low-dose erythromycin study (BLESS). American journal of respiratory and critical care medicine 185,	Publication/ study type (abstract only)
Serisier Dj, Thompson Pj, Greville H, Kolbe J, and Bruinenberg Pr (2011) Dual release ciprofloxacin for inhalation (DRCFI) reduces sputum <i>Pseudomonas aeruginosa</i> (Pa) density and delays time to infective pulmonary exacerbation in non-cystic fibrosis (CF) bronchiectasis (BE). European respiratory society annual congress, amsterdam, the netherlands, and september 24-28 28(55), 334s [1928]	Publication/ study type (abstract only)
Shi Zu-Liang, Peng Hui, Hu Xian-Wei, and Hu Jie-Gui (2014) Effectiveness and safety of macrolides in bronchiectasis patients: a meta-analysis and systematic review. Pulmonary pharmacology & therapeutics 28(2), 171-8	Not relevant population
Sidhu M K, Mandal P, and Hill A T (2014) Bronchiectasis: An update on current pharmacotherapy and future perspectives. Expert Opinion on Pharmacotherapy 15(4), 505-525	Publication/ study type (not relevant study type)
Sidhu Manjit K, Mandal Pallavi, and Hill Adam T (2014) Bronchiectasis: an update on current pharmacotherapy and future perspectives. Expert opinion on pharmacotherapy 15(4), 505-25	Publication/ study type (not relevant study type)
Sidhu Manjit K, Mandal Pallavi, and Hill Adam T (2015) Developing drug therapies in bronchiectasis. Expert opinion on investigational drugs 24(2), 169-81	Publication/ study type (not relevant study type)
Silva Filho, Luiz Vicente Ribeiro Ferreira da, Pinto Leonardo Araujo, and Stein Renato Tetelbom (2015) Use of macrolides in lung diseases: recent literature controversies. Jornal de pediatria 91(6 Suppl 1), S52-60	Publication/ study type (not relevant study type)
Silva Y, Greer T, Farah C, Li F, and Morgan L (2015) Lung flute is comparable to flutter device for adults with non-cystic fibrosis bronchiectasis. Physiotherapy (united kingdom). 101, eS1398	No relevant intervention
Singleton R J, Valery P C, Morris P, Byrnes C A, Grimwood K, Redding G, Torzillo P J, McCallum G, Chikoyak L, Mobberly C, Holman R C, and Chang A B (2014) Indigenous children from three countries with non-cystic fibrosis chronic suppurative lung disease/bronchiectasis. Pediatric Pulmonology 49(2), 189-200	Publication/ study type (not relevant study type)
Snijders D, Calgaro S, Bertozzi I, Quartesan S, Kozuh I, Lunardi F, and Barbato A (2013) Inhaled mucoactive drugs for treating non-cystic fibrosis bronchiectasis in children. International Journal of Immunopathology and Pharmacology 26(2), 529-534	Publication/ study type (no data reported)

Study reference	Reason for exclusion
Snijders D, Calgaro S, Bertozzi I, Quartesan S, Kozuh I, Lunardi F, and Barbato A (2013) Inhaled mucoactive drugs for treating non-cystic fibrosis bronchiectasis in children. International Journal of Immunopathology and Pharmacology 26(2), 529-534	Publication/study type (no data reported)
Soyza A, Aksamit T, Bandel T-J, Criollo M, Elborn Js, Krahn U, Lau M, Operschall E, Polverino E, Winthrop K, and Wilson R (2016) Efficacy and tolerability of ciprofloxacin dry powder for inhalation (ciprofloxacin DPI) in bronchiectasis (non-CF etiology): results from the phase iii respire 1 study. Chest. Conference: CHEST 2016. United states. Conference start: 20161022. Conference end: 20161026 150(4 Supplement 1), 1315a	Publication/study type (abstract only)
Soyza A, Aksamit T, Bandel T-J, Criollo M, Elborn Js, Krahn U, Operschall E, Polverino E, Winthrop K, and Wilson R (2016) Ciprofloxacin DPI 32.5mg b.d. administered 14 day on/off or 28 day on/off vs placebo for 48 weeks in subjects with non-cystic fibrosis bronchiectasis (NCFB). European respiratory journal. Conference: european respiratory society annual congress 2016. United kingdom 48(no pagination),	Publication/study type (abstract only)
Soyza A, Aksamit T, Bandel Tj, Criollo M, Elborn Js, Operschall E, Polverino E, Winthrop K, and Wilson R (2016) Baseline therapies for bronchiectasis (non-CF etiology) vary by country-data from the RESPIRE1 trial of ciprofloxacin dry powder for inhalation (DPI). Pneumologie. Conference: 1st world bronchiectasis conference. Germany. Conference start: 20160707. Conference end: 20160709 70(10) (no pagination),	Publication/study type (abstract only)
Soyza A, Aksamit Tr, Bandel T-J, Criollo M, Elborn J S, and Krahn U (2016) RESPIRE 1: ciprofloxacin DPI 32.5mg b.d. administered 14 day on/off or 28 day on/off vs placebo for 48 weeks in subjects with non-cystic fibrosis bronchiectasis (NCFB). European respiratory journal 48(Suppl 60), Oa272	Publication/study type (abstract only)
Stafler Patrick, and Carr Siobhan B (2010) Non-cystic fibrosis bronchiectasis: its diagnosis and management. Archives of disease in childhood. Education and practice edition 95(3), 73-82	Publication/study type (not relevant study type)
Su C L, Chang C C, Lin Y K, Lee K T, Lee C N, and Chiang L L (2012) Randomized Crossover Study of Lung Expansion Therapy Using Negative Pressure and Positive Pressure in Bronchiectasis. Journal of Experimental and Clinical Medicine 4(3), 149-153	Not relevant intervention
Suresh Babu, K , Kastelik J, and Morjaria J B (2013) Role of long term antibiotics in chronic respiratory diseases. Respiratory medicine 107(6), 800-15	Publication/study type (not relevant study type)
Suresh Babu, K , Kastelik J, and Morjaria J B (2013) Role of long term antibiotics in chronic respiratory diseases. Respiratory Medicine 107(6), 800-815	Publication/study type (not relevant study type)
Tabernero E, Alkiza R, Gil P, Garros J, Cantero D, Artola JI, and Ramos L (2012) Inhaled colistin in elderly patients with bronchiectasis and chronic bronchial infection with pseudomonas. European respiratory journal 40,	Publication/study type (abstract only)

Study reference	Reason for exclusion
Taberbero Huguet E; Gil Alaña P; Alkiza Basañez R; Hernández Gil A; Garros Garay J; Artola Igarza JI; (2015) Inhaled colistin in elderly patients with non-cystic fibrosis bronchiectasis and chronic <i>Pseudomonas aeruginosa</i> bronchial infection. Revista española de geriatría y gerontología 50(3), 111-115	Publication/study type (abstract only)
Tarrant Benjamin J, Le Maitre , Caitlin , Romero Lorena, Steward Ranjana, Button Brenda M, Thompson Bruce R, and Holland Anne E (2017) Mucoactive agents for chronic, non-cystic fibrosis lung disease: A systematic review and meta-analysis. Respirology (Carlton, and Vic.) 22(6), 1084-1092	Excluded after consultation (non-antimicrobial/prevention)
Ten Hacken, N H T, Wijkstra P J, and Kerstjens H A. M (2007) Treatment of bronchiectasis in adults. British Medical Journal 335(7629), 1089-1093	Publication/study type (not relevant study type)
ten Hacken, Nick H T, Wijkstra Peter J, and Kerstjens Huib A. M (2007) Treatment of bronchiectasis in adults. BMJ (Clinical research ed.) 335(7629), 1089-93	Publication/study type (not relevant study type)
Terpstra L, Altenburg J, and Boersma W (2016) Effects of long term tobramycin inhalation solution (TIS) once daiLy on exacerbation rate in patients with non-cystic fibrosis bronchiectasis. A doubleblind, randomized, placebo controlled trial. The BATTLE study. Pneumologie. Conference: 1st world bronchiectasis conference. Germany. Conference start: 20160707. Conference end: 20160709 70(10) (no pagination),	Publication/study type (abstract only)
Thongmak P, Piyavisetpat N, Wongtim S, and Kawkitinarong K (2014) Effects of inhaled salmeterol/fluticasone on lung function in patients with bronchiectasis. European respiratory journal 44,	Publication/study type (abstract only)
Twiss J, and Byrnes C (2009) Nebulised antibiotics reduce symptoms, bacterial density and oral antibiotic usage in children with non cystic fibrosis bronchiectasis. Respirology (carlton, and vic.) 14(Suppl 1), A76	Publication/study type (abstract only)
Twiss J, and Byrnes Ca (2008) Nebulized antibiotics reduce symptoms, bacterial density and oral antibiotic usage in children with non cystic fibrosis bronchiectasis. American thoracic society international conference, may 16-21, 2008, and toronto , A681 [#c40]	Publication/study type (abstract only)
Welsh Emma J, Evans David J, Fowler Stephen J, and Spencer Sally (2015) Interventions for bronchiectasis: an overview of Cochrane systematic reviews. The Cochrane database of systematic reviews (7), CD010337	Publication/study type (not relevant study type)
Whitters D, and Stockley R A (2013) Bronchiectasis in older patients with chronic obstructive pulmonary disease: Prevalence, diagnosis and therapeutic management. Drugs and Aging 30(4), 215-225	Publication/study type (not relevant study type)

Study reference	Reason for exclusion
Wilkinson Mark, Sugumar Karnam, Milan Stephen J, Hart Anna, Crockett Alan, and Crossingham Iain (2014) Mucolytics for bronchiectasis. The Cochrane database of systematic reviews (5), CD001289	Excluded after consultation (non-antimicrobial/prevention)
Wills P, and Greenstone M (2006) Inhaled hyperosmolar agents for bronchiectasis. The Cochrane database of systematic reviews (2), CD002996	Publication/study type (updated version available)
Wilson R, Welte T, Polverino E, Soyza A, Greville H, O'Donnell A, Alder J, Reimnitz P, and Hampel B (2011) Randomized, placebo-controlled, double-blind, multi-center study to evaluate the safety and efficacy of ciprofloxacin dry powder for inhalation (ciprofloxacin DPI) compared with placebo in patients with non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine 183(1 Meeting Abstracts),	Publication/study type (abstract only)
Wong Ca, Jayaram L, Karalus N, Eaton T, Tong C, Hockey H, Milne D, Ferguson W, Tuffery C, Sexton P, Storey L, and Ashton T (2012) Azithromycin decreases exacerbations in non-cystic fibrosis bronchiectasis. American journal of respiratory and critical care medicine 185,	Publication/study type (abstract only)
Yap Vanessa L, and Metersky Mark L (2015) New therapeutic options for noncystic fibrosis bronchiectasis. Current opinion in infectious diseases 28(2), 171-6	Publication/study type (not relevant study type)
Zhuo Guang-Ying, and He Qing (2014) Inaccurate data in my meta-analysis of prolonged macrolides for patients with non-cystic fibrosis bronchiectasis in adult. Pulmonary pharmacology & therapeutics 29(1), 90	Publication/study type (erratum only)
Zoumot Zaid, and Wilson Robert (2010) Respiratory infection in noncystic fibrosis bronchiectasis. Current opinion in infectious diseases 23(2), 165-70	Publication/study type (not relevant study type)

11 Terms used in this guideline

11.1 Acute exacerbation of bronchiectasis

An acute exacerbation of bronchiectasis is characterised by an acute deterioration of normal symptoms and signs usually over several days. It presents with worsening local symptoms (such as cough, increased sputum volume, change of sputum viscosity, or increased sputum purulence) with or without increased wheeze, breathlessness or haemoptysis. Fever or pleurisy may also be present ([British Thoracic Society guideline on non-cystic fibrosis bronchiectasis 2010](#)).

Bronchiectasis is defined as persistent or recurrent bronchial sepsis related to irreversibly damaged and dilated bronchi ([British Thoracic Society guideline on non-cystic fibrosis bronchiectasis 2010](#)). This guideline covers acute exacerbations of bronchiectasis not caused by cystic fibrosis.