NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Guideline

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

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- previous sputum culture and susceptibility results.

1.1.4 When results of sputum culture and susceptibility testing are available:

- review the choice of antibiotic, **and**
- only change the antibiotic according to susceptibility results if bacteria are resistant and symptoms are not already improving (using a narrow spectrum antibiotic wherever possible).

1.1.5 When an antibiotic prescription is given, give advice about:

- possible adverse effects of the antibiotic, particularly diarrhoea
- seeking medical help if symptoms worsen rapidly or significantly at any time, or the person becomes systemically very unwell.

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1.1.6 Reassess the person if symptoms worsen rapidly or significantly at any time, taking account of:

- other possible diagnoses, such as pneumonia
- any symptoms or signs suggesting a more serious illness or condition, such as cardiorespiratory failure or sepsis.
- previous antibiotic use which may have led to resistant bacteria.

Send a repeat sputum sample for culture and susceptibility testing if symptoms have not resolved following antibiotic treatment.

Referral and seeking specialist advice

1.1.7 Refer people with an acute exacerbation of bronchiectasis to hospital if they have:

- cardiorespiratory failure, **or**
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- any of the high risk criteria for severe illness or death from the NICE guideline on sepsis.

1.1.8 Seek specialist advice for an acute exacerbation of bronchiectasis if the person:

- has symptoms that are not improving with repeated courses of antibiotic treatment
- has bacteria that are resistant to oral antibiotics
- cannot take oral medicines (to explore locally available options for giving intravenous antibiotics at home or in the community, rather than in hospital, where this is appropriate).

1 Choice of antibiotic for treating an acute exacerbation of bronchiectasis

1.2.1 When prescribing antibiotic treatment for an acute exacerbation of bronchiectasis:

- follow table 1 for adults aged 18 years and over
- follow table 2 for children and young people under 18 years.

1.2.2 Give oral antibiotics first line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics.

1.2.3 Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible.

Table 1. Antibiotic treatment for adults aged 18 years and over

Antibiotic[1]	**Dosage and course length**
First choice oral antibiotics[2,3]	
Amoxicillin	500 mg three times a day for 7 days then review[4]
Clarithromycin	500 mg twice a day for 7 days then review[4]
Erythromycin	500 mg four times a day for 7 days then review[4]
Doxycycline	200 mg on first day, then 100 mg once a day for a 7-day course in total then review[4]
Second choice oral antibiotics if severely unwell or higher risk of certain pathogens (guided by susceptibilities when available)	
Amoxicillin high-dose (if severe and colonised with *Haemophilus influenzae* [beta-lactamase negative])	1 g three times a day or 3 g twice a day for 7 days then review[4]
Co-amoxiclav (if severe, and **not** colonised with *Pseudomonas aeruginosa*)	500/125 mg three times a day for 7 days then review[4]
Ciprofloxacin (if colonised with *Pseudomonas aeruginosa*; higher dose if severe)	500 mg or 750 mg twice a day for 7 days then review[4]
First choice intravenous antibiotics (if unable to take oral antibiotics or severely unwell; guided by specialist advice and susceptibilities when available)[5]	
Ceftriaxone (**not** if colonised with *Pseudomonas aeruginosa*)	2 g once a day
Co-trimoxazole (**not** if colonised with *Pseudomonas aeruginosa*)[6]	960 mg to 1440 mg twice a day
Ceftazidime	2 g three times a day
Piperacillin with tazobactam	4.5 g three times a day, increased if necessary to 4.5 g four times a day
Ciprofloxacin	400 mg twice or three times a day
Co-amoxiclav	1.2 g three times a day

Second choice intravenous antibiotics or combined therapy
Consult local microbiologist; guided by susceptibilities

[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding.

[2] Empirical treatment or guided by most recent sputum culture and susceptibility.

[3] Amoxicillin or erythromycin are the preferred choices in women who are pregnant.

[4] Review treatment after 7 days and either stop the antibiotic if clinically stable or continue for a further 7 days as appropriate.

[5] Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible for a total antibiotic course of 7 to 14 days.

[6] Co-trimoxazole should only be considered for use in acute exacerbations of bronchiectasis when there is bacteriological evidence of sensitivity and good reason to prefer this combination to a single antibiotic (BNF, June 2018).

Table 2. Antibiotic treatment for children and young people under 18 years

Antibiotic[1]	**Dosage and course length[2]**
First choice oral antibiotics[3,4]	
Amoxicillin	1 to 11 months, 125 mg three times a day for 7 days then review[5] 1 to 4 years, 250 mg three times a day for 7 days then review[5] 5 to 17 years, 500 mg three times a day for 7 days then review[5]
Clarithromycin	1 month to 11 years: Under 8 kg, 7.5 mg/kg twice a day for 7 days then review[5] 8 to 11 kg, 62.5 mg twice a day for 7 days then review[5] 12 to 19 kg, 125 mg twice a day for 7 days then review[5] 20 to 29 kg, 187.5 mg twice a day for 7 days then review[5] 30 to 40 kg, 250 mg twice a day for 7 days then review[5] **or** 12 to 17 years: 250 mg to 500 mg twice a day for 7 days then review[5]
Erythromycin	1 month to 1 year, 125 mg four times a day or 250 mg twice a day for 7 days then review[5] 2 to 7 years, 250 mg four times a day or 500 mg twice a day for 7 days then review[5] 8 to 17 years, 250 mg to 500 mg four times a day or 500 mg to 1,000 mg twice a day for 7 days then review[5]
Doxycycline	12 to 17 years, 200 mg on first day, then 100 mg once a day for a 7-day course in total then review[5]

Antibiotic[1]	**Dosage and course length[2]**
Second choice oral antibiotics if severely unwell or higher risk of certain pathogens (guided by susceptibilities when available)	
Amoxicillin high-dose (if severe and colonised with *Haemophilus influenzae* [beta-lactamase negative])	1 month to 11 years, 30 mg/kg (maximum 1 g per dose) three times a day for 7 days then review[5] 12 to 17 years, 1 g three times a day for 7 days then review[5]
Co-amoxiclav (if severe and **not** colonised with *Pseudomonas aeruginosa*)	1 to 11 months, 0.25 ml/kg of 125/31 suspension three times a day for 7 days then review[5] 1 to 5 years, 5 ml of 125/31 suspension three times a day or 0.25 ml/kg of 125/31 suspension three times a day for 7 days then review[5] 6 to 11 years, 5 ml of 250/62 suspension three times a day or 0.15 ml/kg of 250/62 suspension three times a day for 7 days then review[5] 12 to 17 years, 250/125 mg three times a day or 500/125 mg three times a day for 7 days then review[5]
Ciprofloxacin (on specialist advice if colonised with *Pseudomonas aeruginosa*; higher dose if severe)	1 to 11 years, 20 mg/kg twice daily (maximum 750 mg per dose) for 7 days then review[5] 12 to 17 years, 500 mg or 750 mg twice a day for 7 days then review[5]

Antibiotic[1]	**Dosage and course length**[2]
First choice intravenous antibiotics (if unable to take oral antibiotics or severely unwell; guided by specialist advice and susceptibilities when available)[6]	
Ceftriaxone (**not** if colonised with *Pseudomonas aeruginosa*)	1 month to 11 years (up to 50 kg), 50 to 80 mg/kg once a day (maximum 4 g per day) 9 to 11 years (50 kg and above), 1 to 2 g once a day 12 to 17 years, 1 to 2 g once a day
Co-trimoxazole (**not** if colonised with *Pseudomonas aeruginosa*)[7]	6 weeks to 17 years, 18 mg/kg to 27 mg/kg twice a day (maximum 1440 mg per dose)
Ceftazidime	From 1 month, 25 to 50 mg/kg three times a day (maximum 6 g per day)
Piperacillin with tazobactam	1 month to 11 years, 90 mg/kg three or four times a day (maximum per dose 4.5 g four times a day) 12 to 17 years, 4.5 g three times a day, increased if necessary to 4.5 g four times a day
Ciprofloxacin	1 to 11 years, 10 mg/kg three times a day (maximum 400 mg per dose) 12 to 17 years, 400 mg twice or three times a day
Co-amoxiclav	1 to 2 months, 30 mg/kg twice a day 3 months to 17 years, 30 mg/kg three times a day (maximum 1.2 g three times a day)
Second choice intravenous antibiotic or combined therapy	
Consult local microbiologist; guided by susceptibilities	

[1] See BNF for children for appropriate use and dosing in specific populations, for example hepatic impairment and renal impairment.

[2] The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition and the child's size in relation to the average size of children of the same age.

[3] Empirical treatment or guided by most recent sputum culture and susceptibility.

[4] Amoxicillin or erythromycin are the preferred choices in young women who are pregnant.

[5] Review treatment after 7 days and either stop the antibiotic if clinically stable or continue for a further 7 days as appropriate.

[6] Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible for a total antibiotic course of 7 to 14 days.

[7] Co-trimoxazole should only be considered for use in acute exacerbations of bronchiectasis when there is bacteriological evidence of sensitivity and good reason to prefer this combination to a single antibiotic (BNF for children, June 2018).

Preventing acute exacerbations of bronchiectasis (non-cystic fibrosis)

1.3.1 Do not routinely offer antibiotic prophylaxis to prevent acute exacerbations of bronchiectasis. Give advice about seeking medical help if symptoms of an acute exacerbation develop.

1.3.2 Only consider antibiotic prophylaxis (see the recommendations on choice of antibiotic) for adults with repeated acute exacerbations of bronchiectasis, taking account of evidence that antibiotics can:

- reduce exacerbations
- increase antimicrobial resistance
- cause adverse effects, particularly diarrhoea.

1.3.3 Before antibiotic prophylaxis is given, give advice about:

- the risk of antimicrobial resistance with long-term antibiotics, which may mean fewer effective antibiotics for future exacerbations
- possible adverse effects of long-term antibiotics, particularly diarrhoea, but also less common cardiac events with macrolide antibiotics
- possible interactions of macrolide antibiotics with other medicines
- returning for review after 3 months, or other agreed time

1.3.4 When prescribing antibiotics to prevent acute exacerbations of bronchiectasis follow table 3 for adults aged 18 years and over.

1.3.5 Do not offer nebulised dornase alfa to prevent acute exacerbations of bronchiectasis.

1.3.6 Do not offer inhaled corticosteroids (with or without a long-acting beta2 agonist) for the sole purpose of preventing acute exacerbations of bronchiectasis.

Choice of antibiotic for preventing acute exacerbations

Table 3. Antibiotic prophylaxis for adults aged 18 years and over

Antibiotic prophylaxis[1,2]	**Dosage and course length**[3]
First choice[4]	
Azithromycin	500 mg three times a week or 250 mg daily
Clarithromycin	250 mg twice day
Erythromycin	500 mg twice a day

[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding.

[2] Choose antibiotics according to recent sputum culture and susceptibility results where possible. Select a different antibiotic for prophylaxis if treating an acute exacerbation of bronchiectasis.

[3] Doses given are by mouth using immediate release medicines, unless otherwise stated.

[4] Erythromycin is the preferred choice in women who are pregnant.

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 a worsening cough (with increased sputum volume, viscosity, or purulence) with or without increased wheeze, breathlessness or haemoptysis; and/or fever or pleurisy. The presence of mucopurulent or purulent sputum alone without a deterioration in symptoms is not necessarily an acute exacerbation. 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.

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. 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 (British Thoracic Society guideline for non-CF bronchiectasis 2010).

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

1.1.1 Current guidelines on managing acute exacerbations of bronchiectasis

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. Current guidelines, such as the British Thoracic Society guideline for non-CF bronchiectasis 2010 make recommendations based on old, heterogeneous, studies comparing different antibiotic regimens (often of intramuscular or intravenous antibiotics in hospitalised patients) and expert consensus.

The BTS guideline concluded that this limited evidence base supports the use of high-dose targeted antibiotic therapy for the treatment of an acute exacerbation, with high doses often required to achieve the sputum becoming mucoid and bacterial clearance. They state that symptomatic improvement has generally been seen in studies of 10 to 14-day course lengths, and expert consensus is for a 14-day course for all exacerbations. However, further studies are needed to assess whether shorter treatment durations would be sufficient, particularly in people with mild bronchiectasis. The BTS guideline recommends that antibiotic choice is usually empirical in the first instance, based on the likely pathogen and possibly previous sputum cultures in individual people. Antibiotics can be modified once the pathogen is isolated only if there is no clinical improvement, and treatment should then be guided by susceptibility results. They state that failure to respond to a course of antibiotics requires a repeat sputum culture. Intravenous antibiotics are recommended when people are particularly unwell, have resistant organisms or have not responded to oral therapy (which is most likely in people with *Pseudomonas aeruginosa*).

For the prevention of exacerbations, the BTS guideline recommends that certain adults with a poor exacerbation history can be considered for prophylactic antibiotics. This includes people having at least 3 exacerbations per year requiring antibiotic treatment or those with fewer exacerbations that are causing significant morbidity. They recommend that the choice of antibiotic should be determined by sputum microbiology when clinically stable, and high doses should not be used to minimise side effects. For children, they recommend prophylactic antibiotics can be considered for frequent symptoms or severe disease. However, they also caution

that long-term antibiotics may result in antibiotic resistance in individual patients and alternative antibiotics should be chosen depending on susceptibility results. The BTS guideline also considers long-term treatment with mucoactive agents, such as mucolytics and hyperosmolar agents, bronchodilators and inhaled corticosteroids.

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).

Allergic reactions to penicillins (such as phenoxymethylpenicillin) occur in 1 to 10% of treated people and anaphylactic reactions occur in less than 0.05% (BNF June 2018). People with a history of atopic allergy (for example, asthma, eczema, and hayfever) are at a higher risk of anaphylactic reactions to penicillins. People with a history of immediate hypersensitivity to penicillins may also react to cephalosporins and other beta-lactam antibiotics. See the NICE guideline on drug allergy: diagnosis and management for more information.

Quinolones, 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 (BNF June 2018).

Aminoglycosides are not absorbed from the gut and must be given by injection for systemic infections. Gentamicin is the aminoglycoside of choice in the UK loading and maintenance doses are calculated on the basis of the patient's weight and renal function, with adjustments made according to serum-gentamicin concentrations. Whenever possible treatment should not exceed 7 days. Amikacin is used in the treatment of serious infections caused by gentamicin-resistant Gram-negative bacilli (BNF June 2018).

Co-trimoxazole is currently under restriction for use in the UK. It is advised that it only be used in urinary tract infections (UTI) where there is bacteriological evidence of sensitivity to co-trimoxazole. Co-trimoxazole should be used with caution in those with asthma, or people with blood disorders, GP6D deficiency or infants under 6

weeks (except for treatment or prophylaxis of pneumocystis pneumonia) (BNF June 2018).

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 June 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 June 2018).

Patients must be assessed for bronchial hyperresponsiveness to inhaled mannitol before starting the therapeutic dose regimen; an initiation dose assessment must be carried out under medical supervision (BNF June 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, quinolones 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 mannitol is not licensed for use in bronchiectasis, so use for this indication would be off label.

2 Recommendations

The recommendations in this guideline are for managing and preventing an acute exacerbation in people with non-cystic fibrosis bronchiectasis.

2.1 Managing an acute exacerbation of bronchiectasis (non-cystic fibrosis)

> Be aware that an acute exacerbation of bronchiectasis is a sustained worsening of symptoms from a person's stable state. (Recommendaton 1.1.1)

Rationale

Based on experience, the committee agreed that an acute exacerbation is a sustained worsening of symptoms from a person's stable state. The committee

agreed with the defiintion of an acute exacerbation in the BTS guideline on non-cystic fibrosis bronchiectasis 2010.

Treatment

Obtain a sputum sample from people with an acute exacerbation of bronchiectasis and send for culture and susceptibility testing. (Recommendaton 1.1.2)

Rationale

Based on consensus, the committee agreed that although in the first instance antibiotic treatment will be empirical or based on the most recent sputum culture, a new sputum sample should be sent for culture to confirm susceptibility of the bacteria. The committee discussed that people with bronchiectasis are likely to have previous sputum samples, and because pathogenic bacteria are reasonably static in this population, antibiotics that worked previously are a good starting point to treat new exacerbations. However, pathogenic bacteria can change and a new sputum sample should be sent for culture when people present with a new exacerbation of bronchiectasis.

Consider an antibiotic (see the recommendations on choice of antibiotic) for people with an acute exacerbation of bronchiectasis taking account of:

- the limited evidence base for antibiotics
- the number and severity of symptoms
- previous exacerbation and hospital admission history, and the risk of developing complications
- previous sputum culture and susceptibility results. (Recommendaton 1.1.3)

Rationale

The committee discussed the limited evidence base for antibiotics for treating an acute exacerbation of bronchiectasis. No evidence was found comparing antibiotics with placebo from systematic reviews or randomised controlled trials from the search, which went back to 2006. The committee was aware of UK guidelines that make recommendations for the antimicrobial treatment of acute exacerbations based on older, heterogeneous, head to head studies comparing different antibiotic regimens (often of intramuscular or intravenous antibiotics in hospitalised patients, which may not reflect current practice) and expert consensus. The committee agreed, based on their experience, that people with an acute exacerbation may benefit from antibiotic treatment, but this should be considered on an individual patient basis, based on the number and severity of their symptoms, their previous exacerbation and hospital admission history, their risk of developing complications, and previous sputum culture and susceptibility results. The committee noted that

exacerbations could also be due to a viral infection or environmental factors rather than a bacterial infection.

When results of sputum culture and susceptibility testing are available:

- review the choice of antibiotic, **and**
- only change the antibiotic according to susceptibility results if bacteria are resistant and symptoms are not already improving (using a narrow spectrum antibiotic wherever possible). (Recommendaton 1.1.4)

Rationale

Based on consensus, the committee agreed that when results of sputum cultures are available, if they suggest the bacteria are not susceptible, the person should be contacted to assess symptoms. However, the antibiotic should only be changed according to susceptibility results if symptoms are not already improving. In line with good antimicrobial stewardship, narrow spectrum antibiotics should be used wherever possible.

When an antibiotic prescription is given, give advice about:

- possible adverse effects of the antibiotic, particularly diarrhoea
- seeking medical help if symptoms worsen rapidly or significantly at any time, or the person becomes systemically very unwell. (Recommendaton 1.1.5)

Rationale

The committee agreed that when an antibiotic is given, people should be advised about possible adverse effects and also be given safety netting advice.

Reassessment

Reassess the person if symptoms worsen rapidly or significantly at any time, taking account of:

- other possible diagnoses, such as pneumonia
- any symptoms or signs suggesting a more serious illness or condition, such as cardiorespiratory failure or sepsis
- previous antibiotic use which may have led to resistant bacteria.

Send a repeat sputum sample for culture and susceptibility testing if symptoms have not resolved following antibiotic treatment. (Recommendaton 1.1.6)

Rationale

Based on experience, the committee agreed that, for safety netting, reassessment was needed if symptoms of the acute exacerbation worsen rapidly or significantly at any time.

Referral and seeking specialist advice

Refer people with an acute exacerbation of bronchiectasis to hospital if they have:

- cardiorespiratory failure, **or**
- a severe systemic infection, **or**
- any of the high risk criteria for severe illness or death from the NICE guideline on sepsis. (Recommendaton 1.1.7)

Rationale

Based on experience, the committee agreed that, for safety netting, people with an acute exacerbation of bronchiectasis should be referred to hospital if they have cardiorespiratory failure, a severe systemic infection or suspected sepsis.

Seek specialist advice for an acute exacerbation of bronchiectasis if the person:

- has symptoms that are not improving with repeated courses of antibiotic treatment
- has bacteria that are resistant to oral antibiotics
- cannot take oral medicines (to explore locally available options for giving intravenous antibiotics at home or in the community, rather than in hospital, where this is appropriate). (Recommendaton 1.1.8)

Rationale

The committee discussed that some people with resistant bacteria (particularly *Pseudomonas aeruginosa*) may need intravenous antibiotics, particularly if they are not responding to several courses of oral antibiotics for the same episode, or if several sputum samples show resistance to oral antibiotics. The committee discussed that specialist advice should be sought for people needing intravenous antibiotics, to discuss local options for giving intravenous antibiotics at home or in the community, rather than in hospital, where this is appropriate for the individual.

The committee agreed, based on experience, that it may be necessary to use alternative antibiotics or combine antibiotics in the care of certain people who are severely unwell or have particular pathogens, but this should be done according to local policy on the advice of a microbiologist.

Non-antimicrobial treatment of an acute exacerbation

No recommendation made.

Rationale

The committee considered that no evidence for the non-antimicrobial treatment of an acute exacerbation was found and no recommendations could be made.

The committee was aware of general good practice recommendations to provide personalised self-management plans for people with non-cystic fibrosis bronchiectasis which give advice on recognising the early signs of an exacerbation and ensuring that people know when to take any rescue medication provided, which may include a short-acting beta2-agonist for wheeze or breathlessness.

2.2 Choice of antibiotic for treating an acute exacerbation of bronchiectasis

When prescribing antibiotic treatment for an acute exacerbation of bronchiectasis:

- follow table 1 for adults aged 18 years and over
- follow table 2 for children and young people under 18 years. (Recommendaton 1.2.1)

Rationale

Committee discussion on choice of antibiotic

Very limited evidence was identified to guide the choice of antibiotic for treating an acute exacerbation of bronchiectasis.

Based on experience, common pathogens in acute exacerbations, the susceptibility of these to various classes of antibiotics, the risks of resistance, and good antimicrobial stewardship, the committee agreed the following antibiotic choices. Several oral and intravenous antibiotics were recommended to enable antibiotics to be selected based on the severity of illness and antibiotic susceptibilities from culture results when available.

First-choice **oral antibiotics** are:

- **amoxicillin** (a penicillin) at the usual dose of 500 mg three times a day for adults (with corresponding usual doses in children), which has good activity against common pathogens, such as *Streptococcus pneumoniae* and *Haemophilus influenzae*
- **clarithromycin** or **erythromycin** (macrolides; erythromycin is preferred in women who are pregnant) at usual doses
- **doxycycline** (a tetracycline; adults and young people over 12 years only) at the usual dose.

Second-choice oral antibiotics for people who are more severely unwell or are at higher risk of certain pathogens (guided by susceptibilities when available) are:

- **high-dose amoxicillin** (1 g three times a day or 3 g twice a day for adults; with corresponding doses in children), if severely ill and colonised with beta-lactamase negative *Haemophilus influenzae*

- **co-amoxiclav** (500/125 mg three times a day for adults; with corresponding doses in children), if severely ill and colonised with pathogens other than *Pseudomonas aeruginosa* (this broad-spectrum antibiotic combines a penicillin with a beta-lactamase inhibitor, making it active against beta-lactamase-producing bacteria that are resistant to amoxicillin alone)
- or **ciprofloxacin** (500 mg or 750 mg twice a day; with corresponding doses in children [only on specialist advice because quinolones are generally not recommended in children or young people who are growing], a quinolone which should be reserved for people colonised with *Pseudomonas aeruginosa* only.

First-choice **intravenous antibiotics** at usual doses for treating acute exacerbations in people who are severely unwell, not responding to or unable to take oral antibiotics (guided by specialist advice and susceptibilities when available) are:

- **ceftriaxone** (a third generation cephalosporin), which is suitable for people not colonised with *Pseudomonas aeruginosa*
- **co-trimoxazole** (trimethoprim plus a sulphonamide), which is suitable for people not colonised with *Pseudomonas aeruginosa*
- **ceftazidime** (a third generation cephalosporin)
- **piperacillin with tazobactam** (an antipseudomonal penicillin with a beta-lactamase inhibitor)
- **ciprofloxacin** (a quinolone)
- **co-amoxiclav** (a penicillin with a beta-lactamase inhibitor).

The committee discussed that some people with resistant bacteria (particularly *Pseudomonas aeruginosa*) may need intravenous antibiotics, particularly if they are not responding to several courses of oral antibiotics for the same episode, or if several sputum samples show resistance to oral antibiotics.

The committee discussed that specialist advice should be sought for people needing intravenous antibiotics, to discuss which antibiotics are suitable and the local options for giving intravenous antibiotics at home or in the community, rather than in hospital, where this is appropriate for the individual.

The committee agreed, based on experience, that it may be necessary to use alternative antibiotics or combine antibiotics in the care of certain people who are severely unwell or have particular pathogens, but this should be done according to local policy on the advice of a microbiologist.

The committee discussed evidence from a randomised controlled trial which showed that adding nebulised tobramycin to oral ciprofloxacin did not improve the resolution of exacerbation symptoms, and increased wheeze. The committee agreed that combining a nebulised antibiotic with an oral antibiotic for the treatment of an acute exacerbation added no additional benefit and should not be routinely offered.

Antibiotic course length

Very limited evidence was identified to guide the duration of antibiotics for treating an acute exacerbation of bronchiectasis. The 1 RCT identified, which compared a nebulised antibiotic plus an oral antibiotic with an oral antibiotic alone, used a 14-day course. However, the committee were aware of the British Thoracic Society guideline on non-cystic fibrosis bronchiectasis 2010 which includes older head to head studies comparing different oral, intravenous or intramuscular antibiotic regimens, which used 7-day, 10-day or 14-day courses.

Based on consensus, the committee agreed that the shortest course that is likely to be effective should be prescribed to reduce the risk of antimicrobial resistance and minimise the risk of adverse effects.

The committee agreed that a minimum of a 7-day course of all the recommended antibiotics was required to treat an acute exacerbation. At 7-days, treatment should be reviewed, and either stopped if the person is clinically stable or continued for a further 7 days as appropriate.

Give oral antibiotics first line if the person can take oral medicines, and the severity of their condition does not require intravenous antibiotics. (Recommendaton 1.2.2)

Rationale

Oral antibiotics should be used first-line where possible, in line with antimicrobial stewardship. The committee discussed that some people with resistant bacteria (particularly *Pseudomonas aeruginosa*) may need intravenous antibiotics, particularly if they are not responding to several courses of oral antibiotics for the same episode, or if several sputum samples show resistance to oral antibiotics.

Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible. (Recommendaton 1.2.3)

Rationale

The committee agreed that the use of intravenous antibiotics should be reviewed by 48 hours (taking into account the person's response to treatment and susceptibility results from sputum culture) and switched to oral treatment where possible. This aligns with the NICE guideline on antimicrobial stewardship and Start smart – then focus.

Table 1 Antibiotic treatment for adults aged 18 years and over

Antibiotic[1]	**Dosage and course length**
First choice oral antibiotics[2,3]	
Amoxicillin	500 mg three times a day for 7 days then review[4]
Clarithromycin	500 mg twice a day for 7 days then review[4]
Erythromycin	500 mg four times a day for 7 days then review[4]
Doxycycline	200 mg on first day, then 100 mg once a day for a 7-day course in total then review[4]
Second choice oral antibiotics if severely unwell or higher risk of certain pathogens (guided by susceptibilities when available)	
Amoxicillin high-dose (if severe and colonised with *Haemophilus influenzae* [beta-lactamase negative])	1 g three times a day or 3 g twice a day for 7 days then review[4]
Co-amoxiclav (if severe, and **not** colonised with *Pseudomonas aeruginosa*)	500/125 mg three times a day for 7 days then review[4]
Ciprofloxacin (if colonised with *Pseudomonas aeruginosa*; higher dose if severe)	500 mg or 750 mg twice a day for 7 days then review[4]

Antibiotic[1]	**Dosage and course length**
First choice intravenous antibiotics (if unable to take oral antibiotics or severely unwell;guided by specialist advice and susceptibilities when available)[5]	
Ceftriaxone (**not** if colonised with *Pseudomonas aeruginosa*)	2 g once a day
Co-trimoxazole (**not** if colonised with *Pseudomonas aeruginosa*)[6]	960 mg to 1440 mg twice a day
Ceftazidime	2 g three times a day
Piperacillin with tazobactam	4.5 g three times a day, increased if necessary to 4.5 g four times a day
Ciprofloxacin	400 mg twice or three times a day
Co-amoxiclav	1.2 g three times a day
Second choice intravenous antibiotics, or combined therapy	
Consult local microbiologist; guided by susceptibilities	

[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding.

[2] Empirical treatment or guided by most recent sputum culture and susceptibility.

[3] Amoxicillin or erythromycin are the preferred choices in women who are pregnant.

[4] Review treatment after 7 days and either stop the antibiotic if clinically stable or continue for a further 7 days as appropriate.

[5] Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible for a total antibiotic course of 7 to 14 days.

[6] Co-trimoxazole should only be considered for use in acute exacerbations of bronchiectasis when there is bacteriological evidence of sensitivity and good reason to prefer this combination to a single antibiotic (BNF, June 2018).

Table 2 Antibiotic treatment for children and young people under 18 years

Antibiotic[1]	Dosage and course length[2]
First choice oral antibiotics[3,4]	
Amoxicillin	1 to 11 months, 125 mg three times a day for 7 days then review[5] 1 to 4 years, 250 mg three times a day for 7 days then review[5] 5 to 17 years, 500 mg three times a day for 7 days then review[5]
Clarithromycin	1 month to 11 years: Under 8 kg, 7.5 mg/kg twice a day for 7 days then review[5] 8 to 11 kg, 62.5 mg twice a day for 7 days then review[5] 12 to 19 kg, 125 mg twice a day for 7 days then review[5] 20 to 29 kg, 187.5 mg twice a day for 7 days then review[5] 30 to 40 kg, 250 mg twice a day for 7 days then review[5] **or** 12 to 17 years 250 mg to 500 mg twice a day for 7 days then review[5]
Erythromycin	1 month to 1 year, 125 mg four times a day or 250 mg twice a day for 7 days then review[5] 2 to 7 years, 250 mg four times a day or 500 mg twice a day for 7 days then review[5] 8 to 17 years, 250 mg to 500 mg four times a day or 500 mg to 1,000 mg twice a day for 7 days then review[5]
Doxycycline	12 to 17 years, 200 mg on first day, then 100 mg once a day for a 7-day course in total then review[5]

Antibiotic[1]	Dosage and course length[2]
Second choice oral antibiotics if severely unwell or higher risk of certain pathogens (guided by susceptibilities when available)	
Amoxicillin high-dose (if severe and colonised with *Haemophilus influenzae* [beta-lactamase negative])	1 month to 11 years, 30 mg/kg (maximum 1g per dose) three times a day for 7 days then review[5] 12 to 17 years, 1 g three times a day for 7 days then review[5]
Co-amoxiclav (if severe and **not** colonised with *Pseudomonas aeruginosa*)	1 to 11 months, 0.25 ml/kg of 125/31 suspension three times a day for 7 days then review[5] 1 to 5 years, 5 ml of 125/31 suspension three times a day or 0.25 ml/kg of 125/31 suspension three times a day for 7 days then review[5] 6 to 11 years, 5 ml of 250/62 suspension three times a day or 0.15 ml/kg of 250/62 suspension three times a day for 7 days then review[5] 12 to 17 years, 250/125 mg three times a day or 500/125 mg three times a day for 7 days then review[5]
Ciprofloxacin (on specialist advice if colonised with *Pseudomonas aeruginosa*; higher dose if severe)	1 to 11 years, 20 mg/kg twice daily (maximum 750 mg per dose) for 7 days then review[5] 12 to 17 years, 500 mg or 750 mg twice a day for 7 days then review[5]

Antibiotic[1]	**Dosage and course length**[2]
First choice intravenous antibiotic (if unable to take oral antibiotics or severely unwell). Antibiotics may be combined if sepsis a concern (guided by specialist advice and susceptibilities when available)[6]	
Ceftriaxone (**not** if colonised with *Pseudomonas aeruginosa*)	1 month to 11 years (up to 50 kg), 50 to 80 mg/kg once a day (maximum 4 g per day) 9 to 11 years (50 kg and above), 1 to 2 g once a day 12 to 17 years, 1 to 2 g once a day
Co-trimoxazole (**not** if colonised with *Pseudomonas aeruginosa*)[7]	6 weeks to 17 years, 18 mg/kg to 27 mg/kg twice a day (maximum 1440 mg per dose)
Ceftazidime	From 1 month, 25 to 50 mg/kg three times a day (maximum 6 g per day)
Piperacillin with tazobactam	1 month to 11 years, 90 mg/kg three or four times a day (maximum per dose 4.5 g four times a day) 12 to 17 years, 4.5 g three times a day, increased if necessary to 4.5 g four times a day
Ciprofloxacin	1 to 11 years, 10 mg/kg three times a day (maximum 400 mg per dose) 12 to 17 years, 400 mg twice or three times a day
Co-amoxiclav	1 to 2 months, 30 mg/kg twice a day 3 months to 17 years, 30 mg/kg three times a day (maximum 1.2 g three times a day)
Second choice intravenous antibiotic, or combined therapy	
Consult local microbiologist; guided by susceptibilities	

[1] See BNF for children for appropriate use and dosing in specific populations, for example hepatic impairment and renal impairment.

[2] The age bands apply to children of average size and, in practice, the prescriber will use the age bands in conjunction with other factors such as the severity of the condition and the child's size in relation to the average size of children of the same age.

[3] Empirical treatment or guided by most recent sputum culture and susceptibility.

[4] Amoxicillin or erythromycin are the preferred choices in young women who are pregnant.

[5] Review treatment after 7 days and either stop the antibiotic if clinically stable or continue for a further 7 days as appropriate.

[6] Review intravenous antibiotics by 48 hours and consider stepping down to oral antibiotics where possible for a total antibiotic course of 7 to 14 days.

[7] Co-trimoxazole should only be considered for use in acute exacerbations of bronchiectasis when there is bacteriological evidence of sensitivity and good reason to prefer this combination to a single antibiotic (BNF for children, June 2018).

2.3 Preventing acute exacerbations of bronchiectasis (non-cystic fibrosis)

Do not routinely offer antibiotic prophylaxis to prevent acute exacerbations of bronchiectasis. Give advice about seeking medical help if symptoms of an acute exacerbation develop. (Recommendation 1.3.1)

Rationale

The committee discussed the evidence for prophylactic antibiotics. Overall, antibiotics reduced exacerbation rates, hospitalisations and the number of people with an exacerbation. However, there was a significant increase in antibiotic resistance and adverse effects.

The majority of the studies were in populations who had experienced multiple exacerbations in the previous year and the committee thought the findings could not be generalised to everyone with bronchiectasis.

Based on evidence and experience, the committee agreed that all people should not routinely be offered antibiotic prophylaxis to prevent acute exacerbations, because of the risk/benefit balance in the overall population.

Only consider antibiotic prophylaxis (see the recommendations on choice of antibiotic) for adults with repeated acute exacerbations of bronchiectasis, taking account of evidence that antibiotics can:

- reduce exacerbations
- increase antimicrobial resistance
- cause adverse effects, particularly diarrhoea. (Recommendation 1.3.2)

Rationale

Based on evidence and experience, the committee agreed that although routine antibiotic prophylaxis is not recommended, this could be considered for adults with repeated exacerbations, where the benefits of prophylaxis may outweigh the risks.

The committee discussed the evidence for prophylactic antibiotics. Most evidence was found for oral macrolide antibiotics in adults, where they reduced exacerbation rates and the number of people with an exacerbation. However, they also increased antibiotic resistance and adverse effects. Nebulised or inhaled prophylactic antibiotics had no effect on exacerbations in adults. In 1 small trial of nebulised tobramycin, a non-significant increase in exacerbations, and adverse events such as dyspnoea, chest pain and wheeze were seen.

The majority of the studies were in populations who had experienced multiple exacerbations in the previous year. However, the populations had a variety of exacerbation histories with no clear benefit seen in a specific population. The committee felt it was, therefore, difficult to give a precise definition of 'repeated exacerbations'. Clinical judgement would be needed to define this on an individualised patient basis, taking into account the frequency and severity of exacerbations, and the individualised risks and benefits of long-term antibiotics.

The limited evidence in children and young people found prophylactic oral macrolide antibiotics had no effect on exacerbations but increased antimicrobial resistance, and no recommendation for prophylaxis in children and young people was made.

Before antibiotic prophylaxis is given, give advice about:

- the risk of antimicrobial resistance with long-term antibiotics, which may mean fewer effective antibiotics for future exacerbations
- possible adverse effects of long-term antibiotics, particularly diarrhoea, but also less common cardiac events with macrolide antibiotics
- possible interactions of macrolide antibiotics with other medicines
- returning for review after 3 months, or other agreed time. (Recommendation 1.3.3)

Rationale

The committee agreed that before antibiotic prophylaxis is given, people should be advised about the harms of long-term antibiotics. There is an increased risk of

resistance with long-term antibiotics, which impacts at both a population and an individual level. People should be advised that this can mean fewer antibiotics may work for their exacerbations in the future. People should also be advised about possible common adverse effects, such as diarrhoea, but also about less common cardiac adverse events. They should also be advised about the potential for macrolide antibiotics, in particular, to interact with other medicines. The committee agreed that anyone being offered antibiotic prophylaxis should return for a review after 3 months, or other agreed time.

When prescribing antibiotics to prevent acute exacerbations of bronchiectasis follow table 3 for adults aged 18 years and over. (Recommendation 1.3.4)

Rationale

The committee discussed that the evidence of benefit for antibiotic prophylaxis was with oral macrolides (which included azithromycin, clarithromycin, erythromycin and roxithromycin [not available in the UK]). They discussed that macrolides may have anti-inflammatory or intracellular effects which is why they may show benefit over other antimicrobials. Nebulised or inhaled antibiotics (not all of which are available in the UK) had no effect on exacerbations. However, the evidence base was limited with low patient numbers in all studies.

Based on the evidence, the committee recommended azithromycin (500 mg three times a week or 250 mg daily), clarithromycin 250 mg twice day or erythromycin 500 mg twice a day where antibiotic prophylaxis was considered appropriate. Nebulised or inhaled antibiotics were not recommended.

Do not offer nebulised dornase alfa to prevent acute exacerbations of bronchiectasis. (Recommendation 1.3.5)

Rationale

Evidence showed that nebulised dornase alfa increased exacerbation rates in adults with bronchiectasis, and resulted in more people using antibiotics and steroids. Therefore the committee agreed that nebulised dornase alfa should not be offered to prevent acute exacerbations of bronchiectasis.

Do not offer inhaled corticosteroids (with or without a long-acting beta2 agonist) for the sole purpose of preventing acute exacerbations of bronchiectasis. (Recommendation 1.3.6)

Rationale

Evidence showed that inhaled corticosteroids (with or without a long-acting beta2 agonist) had no effect on acute exacerbations of bronchiectasis in adults. Based on experience, the committee also discussed the potential for adverse effects with inhaled corticosteroids. Therefore the committee agreed that inhaled corticosteroids should not be offered solely to prevent acute exacerbations.

Mannitol

No recommendation made.

Rationale

The committee discussed the limited evidence for inhaled mannitol, which was for use in adults. This found that inhaled mannitol increased the time to first exacerbation and reduced the number of people experiencing an exacerbation. However, this was compared with a lower dose mannitol control group not placebo. The committee also recognised potential issues with the use of mannitol, including:

- it can cause bronchospasm, and people must be assessed for bronchial hyperresponsiveness before treatment, with a supervised initiation dose assessment (BNF June 2018)
- it is not licensed for use in people with bronchiectasis, and use would be off-label.
- it may be difficult for people to use correctly; the dose for cystic fibrosis requires inhaling the contents of 10 capsules via an inhaler device twice a day.
- the cost of 280 inhalation powder capsules with 2 devices is £231.66 (BNF June 2018).

Based on this, the committee agreed not to make a recommendation on the use of mannitol to prevent acute exacerbations.

Other mucoactive agents

No recommendation made.

Rationale

The committee discussed that no evidence relating to exacerbation end points for nebulised hypertonic saline, carbocysteine or erdosteine was found and no recommendations could be made.

2.4 Choice of antibiotic for preventing acute exacerbations

Table 3. Antibiotic prophylaxis for adults aged 18 years and over

Antibiotic prophylaxis[1,2]	Dosage and course length[3]
First choice[4]	
Azithromycin	500 mg three times a week or 250 mg daily
Clarithromycin	250 mg twice day
Erythromycin	500 mg twice a day

[1] See BNF for appropriate use and dosing in specific populations, for example, hepatic impairment, renal impairment, pregnancy and breast-feeding.

[2] Choose antibiotics according to recent sputum culture and susceptibility results where possible. Select a different antibiotic for prophylaxis if treating an acute exacerbation of bronchiectasis.

[3] Doses given are by mouth using immediate release medicines, unless otherwise stated.

[4] Erythromycin is the preferred choice in women who are pregnant.

3 Evidence

The evidence identified in this guideline is for non-antimicrobial and antimicrobial interventions for managing and preventing acute exacerbations of non-cystic fibrosis bronchiectasis, for outcomes relating to exacerbations and safety. Physical therapies, such as airway clearance techniques, were out of scope of this guideline, as were outcomes related to the management of stable bronchiectasis, for example symptoms in stable state bronchiectasis and lung function.

3.1 Treatment of acute exacerbations of bronchiectasis

3.1.1 Non-pharmacological interventions

No systematic reviews or RCTs were found that investigated non-pharmacological interventions for the treatment of acute exacerbations of bronchiectasis.

3.1.2 Non-antimicrobial pharmacological interventions

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

3.1.3 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. There was no evidence in children or young people, and no randomised placebo-controlled trials of antibiotics were identified.

3.1.3.1 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 Importance: Critical	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
		Difference: **204 fewer** per 1000 (CI 95% 387 fewer - 84 more)			
Resolution of exacerbation Day 42 Importance: Critical	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
		Difference: **98 fewer** per 1000 (CI 95% 266 fewer - 235 more)			
Eradication of *Pseudomonas aeruginosa* Importance: Critical	Relative risk 1.88 (CI 95% 0.73 - 4.79) Based on data from 49 patients in 1 study	**200** per 1000	**376** per 1000	**Very Low** Due to serious inconsistency, Due to very serious imprecision[3]	We are uncertain whether oral ciprofloxacin plus nebulised tobramycin increases or decreases eradication of *Pseudomonas aeruginosa*
		Difference: **176 more** per 1000 (CI 95% 54 fewer - 758 more)			
Adverse events Importance: Critical	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
		Difference: **116 fewer** per 1000 (CI 95% 260 fewer - 48 more)			
Adverse event - wheeze Importance: Critical	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
		Difference: **352 more** per 1000 (CI 95% 38 more - 1187 more)			

[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**.

[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**.

[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**.

[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**.

[5] **Risk of bias: No serious**. **Inconsistency: Serious**. N/A; **Indirectness: No serious**. **Imprecision: No serious**. **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

3.2 Prevention of acute exacerbations of bronchiectasis

3.2.1 Non-pharmacological interventions

No systematic reviews or RCTs were found that investigated non-pharmacological interventions for the prevention of acute exacerbations of bronchiectasis.

3.2.2 Non-antimicrobial pharmacological interventions

3.2.2.1 Mucoactive agents

The evidence identified for mucoactive agents for preventing acute exacerbations, for outcomes relating to exacerbations and safety, was for inhaled mannitol and nebulised dornase alfa. No evidence on exacerbation end points was found for nebulised hypertonic saline, carbocysteine or erdosteine.

GRADE profile - Inhaled mannitol versus placebo or control in adults with stable state bronchiectasis

Summary

The evidence review for inhaled mannitol is based on 1 systematic review of 2 double-blind RCTs in adults with stable state bronchiectasis. One study (n=362) compared 320 mg mannitol twice a day with placebo for 12 weeks and the other study (n=461) compared 400 mg mannitol twice a day with 50 mg mannitol twice a day (which the authors reported to be a non-therapeutic dose) for 52 weeks.

Participants in the 52-week study had to have a minimum of 2 pulmonary exacerbations in the past year and at least 4 exacerbations in the previous 2 years. In this RCT, participants were excluded if they failed the mannitol tolerance test 2 to 5 weeks before starting the study.

There was no significant difference between mannitol and placebo in the rate of exacerbations (rate ratio 0.92; 95% CI 0.78 to 1.08; moderate quality evidence), but mannitol significantly increased the time to first exacerbation (median time to exacerbation 165 days for mannitol and 124 days for placebo; HR 0.78, 95% CI 0.63 to 0.96; low quality evidence). Fewer participants also had an exacerbation with mannitol compared with placebo (68.7% compared with 78.1%; RR 0.88, 95% CI 0.79 to 0.98; moderate quality evidence). And the number of days on antibiotics was reduced in the mannitol group (rate ratio 0.76; 95% CI 0.58 to 1.00, p=0.0496; low quality evidence).

There was no significant difference in adverse events or serious adverse events between the groups.

No systematic reviews or RCTs were identified which investigated inhaled mannitol 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 control	**Inhaled mannitol**		
Participants with exacerbations Importance: Critical	Relative risk 0.88 (CI 95% 0.79 - 0.98) Based on data from 461 patients in 1 study	**781** per 1000	**687** per 1000 Difference: **94 fewer** per 1000 (CI 95% 164 fewer - 16 fewer)	**Moderate** Due to serious inconsistency[1]	Inhaled mannitol probably decreases participants with exacerbations
Adverse events Importance: Critical	Relative risk 0.99 (CI 95% 0.95 - 1.03) Based on data from 804 patients in 2 studies	**472** per 1000	**467** per 1000 Difference: **5 fewer** per 1000 (CI 95% 24 fewer - 14 more)	**Moderate** Due to serious inconsistency[2]	Inhaled mannitol may have little or No effect on adverse events
Serious adverse events Importance: Critical	Relative risk 0.82 (CI 95% 0.59 - 1.16) Based on data from 804 patients in 2 studies	**168** per 1000	**138** per 1000 Difference: **30 fewer** per 1000 (CI 95% 69 fewer - 27 more)	**Moderate** Due to very serious imprecision, Due to serious imprecision[3]	Inhaled mannitol probably has little or no effect on serious adverse events

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
		Placebo or control	**Inhaled mannitol**		
Hospitalisations for exacerbations Importance: Critical	Based on data from 461 patients in 1 study Follow up: 12 months	Rate ratio 0.61 (95% CI, 0.34 to 1.09). The authors reported 0.14 hospitalisations per year in the mannitol group compared with 0.20 hospitalisations per year in the placebo group (p=0.1798)		**Low** Due to serious inconsistency, Due to serious imprecision[4]	Inhaled mannitol may have little or no effect on hospitalisations for exacerbations
Number of days on antibiotics[5] Importance: Critical	Based on data from 461 patients in 1 study Follow up: 12 months	Rate ratio 0.76 (95% CI, 0.58 to 1.00) p=0.0496		**Low** Due to serious inconsistency, Due to serious imprecision[6]	Inhaled mannitol may have little or no effect on the number of days on antibiotics
Time to first exacerbation Importance: Critical	Based on data from 461 patients in 1 study Follow up: 56 weeks	Time to first exacerbation was longer in the mannitol group compared with the placebo group (hazard ratio 0.78 [95% CI, 0.63 to 0.96]), median time to exacerbation 165 days for mannitol and 124 days for placebo.		**Low** Due to serious inconsistency, Due to serious imprecision[7]	Inhaled mannitol may increase the time to first exacerbation
Annual rate of exacerbations Importance: Critical	Based on data from 461 patients in 1 study Follow up: 12 months	Rate ratio 0.92 (95% CI, 0.78 to 1.08)		**Moderate** Due to serious inconsistency[8]	Inhaled mannitol probably has little or no effect on annual rate of exacerbations

[1] **Risk of bias: No serious. Inconsistency: Serious.** Not applicable.**; Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

[2] **Risk of bias: No serious. Inconsistency: Serious.** The direction of the effect is not consistent between the included studies; **Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

[3] **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 meaningful difference or appreciable benefit/harm with inhaled mannitol; **Publication bias: No serious.**

[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 or appreciable benefit/harm with inhaled mannitol; **Publication bias: No serious.**

[5] The number of days on antibiotics was reduced by 6.15 days over a year, baseline antibiotic use was not available. ;

[6] **Risk of bias: No serious. Inconsistency: Serious.** The direction of the effect is not consistent between the included studies; **Indirectness: No serious. Imprecision: Serious.** At a minimal important difference (MID) of 25%, data are consistent with no meaningful difference with inhaled mannitol; **Publication bias: No serious.**

[7] **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 inhaled mannitol; **Publication bias: No serious.**

[8] **Risk of bias: No serious. Inconsistency: Serious.** N/A**; Indirectness: No serious. Imprecision: No serious. Publication bias: No serious.**

References

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

GRADE profile - Dornase alfa versus placebo in adults with stable state bronchiectasis

Summary

The evidence review for nebulised dornase alfa (RhDNase) is based on 2 double-blind, placebo-controlled RCTs in adults with stable state bronchiectasis, from 1 systematic review. Participants in one trial (n=61) were randomised to nebulised dornase alfa 2.5 mg once a day, nebulised dornase alfa 2.5 mg twice a day or nebulised placebo, for 2 weeks. Participants in the other trial (n=349) were randomised to 2.5 mg nebulised dornase alfa twice a day or nebulised placebo for 24 weeks.

Dornase alfa 2.5 mg twice daily significantly increased exacerbation rates compared with placebo in the 24-week trial (rate ratio 1.35 (95% CI 1.01 to 1.79; very low quality evidence). However, the number of participants with an exacerbation was not reported. In the 2 week trial there was an increase in hospitalisations in the dornase alfa 2.5 mg twice a day group compared with the placebo group (10% in the dornase alfa group and 0% in the placebo group; RR 5.00 [95% CI 0.26 to 98.00]; very low quality evidence) and hospitalisation rates were increased in the dornase alfa 2.5 mg twice daily group compared with the placebo group in the 24 week trial (0.39 in the dornase alfa group compared with 0.21 in the placebo group ; rate ratio 1.85 [confidence intervals were not included in the trial report]; very low quality evidence).

Both studies reported the number of deaths, but there were too few events owing to the study size and length of study to assess any difference between groups.

Dornase alfa 2.5 mg twice daily significantly increased antibiotic and steroid use compared to the placebo group.

No evidence on adverse events was available. However, there was a significant increase in antibodies to dornase alfa in the treatment group of the 24-week trial.

No systematic reviews or RCTs were identified which investigated dornase alfa 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	**Dornase alfa**		
Hospitalisations for infective exacerbations (2.5 mg once a day) Importance: Critical	Relative risk (CI 95% -) Based on data from 40 patients in 1 study	**0** per 1000	**0** per 1000	**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision[1]	There were too few who experienced hospitalisations for infective exacerbations, to determine whether dornase alfa made a difference
		Difference: **0 fewer** per 1000 (CI 95% 0 fewer - 0 fewer)			
Hospitalisations for infective exacerbations (2.5 mg twice a day) Importance: Critical	Relative risk 5.00 (CI 95% 0.26 - 98.00) Based on data from 40 patients in 1 study	**24** per 1000	**120** per 1000	**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision[2]	There were too few who experienced hospitalisations for infective exacerbations, to determine whether dornase alfa made a difference
		Difference**: 96 more** per 1000 (CI 95% 18 fewer - 2328 more)			
Deaths (2.5 mg once a day) Importance: Critical	Relative risk (CI 95% -) Based on data from 41 patients in 1 study	**0** per 1000	**0** per 1000	**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision[3]	There were too few deaths, to determine whether dornase alfa made a difference
		Difference: **0 fewer** per 1000 (CI 95% 0 fewer - 0 fewer)			
Antibodies to dornase alfa (2.5 mg twice a day) Importance: Critical	Relative risk 24.42 (CI 95% 3.34 - 178.50) Based on data from 349 patients in 1 study	**6** per 1000	**147** per 1000	**Low** Due to serious risk of bias, Due to serious inconsistency[4]	Dornase alfa may increase antibodies to dornase alfa
		Difference: **141 more** per 1000 (CI 95% 14 more - 1065 more)			
Deaths (2.5 mg twice a day) Importance: Critical	Relative risk 3.05 (CI 95% 0.32 - 29.06) Based on data from 389 patients in 2 studies	**5** per 1000	**15** per 1000	**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to very serious imprecision[5]	There were too few deaths, to determine whether dornase alfa made a difference
		Difference: **10 more** per 1000 (CI 95% 3 fewer - 140 more)			
Exacerbation rate (2.5 mg twice a day) Importance: Critical	Based on data from 349 patients in 1 study Follow up: 24 weeks	The protocol and non-protocol defined exacerbation rate was significantly higher in the dornase alfa group than the placebo group (rate ratio 1.35 [95% CI 1.01 to 1.79]).		**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[7]	We are uncertain whether dornase alfa increases or decreases exacerbation rate

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
		Placebo	**Dornase alfa**		
Steroid use (2.5 mg twice a day) Importance: Critical	Based on data from 349 patients in 1 study Follow up: 24 weeks	Steroid use was higher in the dornase alfa group than the placebo group (29.4 vs 56.9 days, p≤0.05)		**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[8]	We are uncertain whether dornase alfa increases or decreases steroid use
Antibiotic use (2.5 mg twice a day) Importance: Critical	Based on data from 349 patients in 1 study Follow up: 24 weeks	Antibiotic use was higher in the dornase alfa group than the placebo group (56.9 vs 44.1 days, p≤0.05)		**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[9]	We are uncertain whether dornase alfa increases or decreases antibiotic use
Hospitalisation rates (2.5 mg twice a day) Importance: Critical	Based on data from 349 patients in 1 study Follow up: 24 weeks	Hospitalisation rates ere higher in the dornase alfa group compared with placebo (0.21 in the placebo group compared with 0.39 in the dornase alfa group; rate ratio 1.85, confidence intervals were not included in the trial report)		**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[10]	We are uncertain whether dornase alfa increases or decreases hospitalisation rates

1. **Risk of bias: Serious**. Random sequence generation and allocation concealment method not reported. ; **Inconsistency: Serious**. Not applicable - single RCT.; **Indirectness: No serious**. **Imprecision: Very serious**. No events in intervention or control group. ; **Publication bias: No serious**.
2. **Risk of bias: Serious**. Random sequence generation and allocation concealment method not reported. ; **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 dornase alfa. ; **Publication bias: No serious**.
3. **Risk of bias: Serious**. Random sequence generation and allocation concealment method not reported. ; **Inconsistency: Serious**. Not applicable - single RCT.; **Indirectness: No serious**. **Imprecision: Very serious**. Not assessable. ; **Publication bias: No serious**.
4. **Risk of bias: Serious**. Random sequence generation and allocation concealment method not reported. ; **Inconsistency: Serious**. Not applicable - single RCT.; **Indirectness: No serious**. **Imprecision: No serious**. **Publication bias: No serious**.
5. **Risk of bias: Serious**. Random sequence generation and allocation concealment methods not reported. ; **Inconsistency: Serious**. Not assessable. ; **Indirectness: No serious**. **Imprecision: Very serious**. Non-significant effect, 95% CI of RR crosses null. ; **Publication bias: No serious**.
6. Relative risk 1.35 95% CI 1.01 to 1.79;
7. **Risk of bias: Serious**. Random sequence generation and allocation concealment methods not reported. ; **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 benefit/harm with dornase alfa; **Publication bias: No serious**.
8. **Risk of bias: Serious**. Random sequence generation and allocation concealment method not reported.; **Inconsistency: Serious**. Not applicable - single RCT.; **Indirectness: No serious**. **Imprecision: Serious**. Not assessable.; **Publication bias: No serious**.
9. **Risk of bias: Serious**. Random sequence generation and allocation concealment method not reported.; **Inconsistency: Serious**. Not applicable - single RCT.; **Indirectness: No serious**. **Imprecision: Serious**. Not assessable.; **Publication bias: No serious**.
10. **Risk of bias: Serious**. Random sequence generation and allocation concealment method not reported.; **Inconsistency: Serious**. Not applicable - single RCT.; **Indirectness: No serious**. **Imprecision: Serious**. Not assessable.; **Publication bias: No serious**.

References

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

3.2.2.2 Inhaled bronchodilators

No systematic reviews or RCTs were found that investigated inhaled bronchodilators, such as beta2 agonists (alone) or anticholinergics, for the prevention of acute exacerbations of bronchiectasis.

3.2.2.3 Inhaled corticosteroids

GRADE profile - Inhaled steroids versus placebo or no treatment in adults with stable state bronchiectasis

Summary

The evidence review for inhaled corticosteroids is based on 1 systematic review of 6 RCTs. All studies were double-blind, placebo-controlled trials with the exception of 1 study which compared inhaled corticosteroids with no treatment. All RCTs were in adults with stable state bronchiectasis which was defined as free from exacerbation for 4 weeks (2 studies) or stable 24-hour sputum volume, forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC).

In the 3 studies that had exacerbation as an outcome, this was defined as persistent deterioration (>24 hours) in at least 3 of the following respiratory symptoms: cough, dyspnoea, haemoptysis, increased sputum purulence or volume, and chest pain.

Only 1 study (n=62) provided data on the average number of exacerbations in the short-term group (inhaled corticosteroids for <6 months) and there was no significant difference between the inhaled corticosteroid group and the no treatment group. Likewise, in the 1 study (n=86) in the long-term group (inhaled corticosteroids for >6 months) there was no significant difference in the average number of exacerbations between groups.

No evidence on adverse events was available.

No systematic reviews or RCTs were identified which investigated inhaled corticosteroids 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 no treatment	**Inhaled corticosteroid**		
Average number of exacerbations per participant (stable-state short-term, <6 months) Importance: Critical	Lower better Based on data from 57 patients in 1 study	**0.31** (Mean)	**1.4** (Mean)	**Very Low** Due to very serious imprecision, Due to very serious risk of bias, Due to serious inconsistency[1]	We are uncertain whether inhaled corticosteroid increases or decreases the average number of exacerbations per participant
		Difference: **MD 0.09 higher** (CI 95% 0.61 lower - 0.79 higher)			
Average number of exacerbations per participant (stable-state long-term, >6 months) Importance: Critical	Lower better Based on data from 86 patients in 1 study	**0.72** (Mean)	**2.23** (Mean)	**Very Low** Due to very serious imprecision, Due to very serious risk of bias, Due to serious inconsistency[2]	We are uncertain whether inhaled corticosteroid increases or decreases the average number of exacerbations per participant
		Difference: **MD 0.49 lower** (CI 95% 1.49 lower - 0.51 higher)			

[1] **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: Serious**. Not applicable - single RCT. ; **Indirectness: No serious**. **Imprecision: Very serious**. At a minimal important difference of 0.5 x STD, data are consistent with no meaningful difference, appreciable benefit or appreciable harm.; **Publication bias: No serious**.

[2] **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; **Inconsistency: Serious**. Not applicable - single RCT.; **Indirectness: No serious**. **Imprecision: Very serious**. At a minimal important difference of 0.5 x STD, data are consistent with no meaningful difference, appreciable benefit or appreciable harm; **Publication bias: No serious**.

References

Kapur Nitin, Bell Scott, Kolbe John, and Chang Anne B (2009) Inhaled steroids for bronchiectasis. The Cochrane database of systematic reviews (1), CD000996

3.2.2.4 Inhaled corticosteroids plus long-acting beta2 agonists

GRADE profile - Medium-dose budesonide plus formoterol versus high-dose budesonide in adults with stable state bronchiectasis

Summary

The evidence review for inhaled corticosteroids plus long-acting beta2 agonists is based on 1 systematic review, which included 1 RCT. The trial included 40 adults with stable non-cystic fibrosis bronchiectasis without co-existing asthma who initially

received 3 months of high-dose inhaled corticosteroids (budesonide 1600 micrograms daily). Participants were then randomised to either a combined inhaled corticosteroid plus long-acting beta2 agonist (medium-dose budesonide 640 micrograms plus formoterol 18 micrograms daily) or a high-dose inhaled corticosteroid (budesonide 1600 micrograms daily) for a further 3 months. The study was not blinded.

After 3 months, no significant difference was seen between groups in the number of hospitalisations due to an exacerbation.

As this was a small, single study with inadequate blinding, the results should be interpreted with caution. It is also difficult to determine the effect of medium-dose budesonide plus formoterol because it was compared with high-dose budesonide, rather than medium-dose budesonide or placebo. Participants were required to stop all other drugs before the start of the trial which may have artificially inflated the baseline clinical measurements.

The authors reported 12 adverse events in the medium-dose budesonide plus formoterol group and 37 adverse events in the high-dose budesonide group, however the number of individuals experiencing adverse events was not reported.

No systematic reviews or RCTs were identified that investigated inhaled corticosteroids plus long-acting beta2 agonists 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**
		High-dose budesonide	**Medium-dose budesonide plus formoterol**		
Hospitalisations due to an exacerbation[1] Importance: Critical	Relative risk 0.30 (CI 95% 0.03 - 2.63) Based on data from 40 patients in 1 study Follow up: 3 months.	**167** per 1000	**50** per 1000 Difference: **117 fewer** per 1000 (CI 95% 162 fewer - 272 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision, Due to serious inconsistency[2]	We are uncertain whether medium-dose budesonide with formoterol increases or decreases hospitalisations due to an infective exacerbation

[1] Number of participants with 1 or more exacerbations (hospitalisations);

[2] **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**. 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 inhaled medium dose budesonide and formoterol. ; **Publication bias: No serious**.

References

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

3.2.3 Antimicrobial interventions

3.2.3.1 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 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 inlcuded 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	**119** per 1000	**Low** Due to very serious imprecision[3]	Antibiotics may have little or no difference on withdrawals due to intolerable side effects
		Difference: **13 fewer** per 1000 (CI 95% 50 fewer - 42 more)			
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	**182** per 1000	**Low** Due to serious risk of bias, Due to serious imprecision[4]	Antibiotics may increase diarrhoea
		Difference: **119 more** per 1000 (CI 95% 15 more - 360 more)			
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	**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
		more per 1000 (CI 95% 24 fewer - 270 more)			
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	**169** per 1000	**Low** Due to serious inconsistency, Due to serious imprecision[6]	Antibiotics may have little or no effect on wheeze
		Difference: **156 more** per 1000(CI 95% 3 fewer - 2883 more)			
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	**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
		Difference: 19 more per 1000 (CI 95% 6 fewer - 437 more)			

Outcome Timeframe	**Study results and measurements**	**Absolute effect estimates**		**Certainty in effect estimates** (Quality of evidence)	**Plain text summary**
		Placebo or standard care	**Antibiotics**		
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	**75** per 1000 Difference: **64 fewer** per 1000 (CI 95% 135 fewer - 1323 more)	**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	**98** per 1000 Difference: **4 fewer** per 1000 (CI 95% 63 fewer - 150 more)	**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	**179** per 1000 Difference: **18 fewer** per 1000 (CI 95% 67 fewer - 49 more)	**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 Importance: Critical	Odds ratio 2.24 (CI 95% 0.74 - 6.83) Based on data from 189 patients in 2 studies	**52** per 1000	**109** per 1000 Difference: **57 more** per 1000 (CI 95% 13 fewer - 221 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[11]	We are uncertain whether antibiotics 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 Difference: **2 more** per 1000 (CI 95% 5 fewer - 35 more)	**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 Difference: 99 more per 1000 (CI 95% **9 more** - 285 more)	**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

3.2.3.2 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 analyis of 8 RCTs from 1 systematic review. The antibiotics used were azithromycin (3 studies), roxithromycin (1 study), erythromycin (2 studies), amoxycillin (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)			

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**		
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	Relative risk 0.88 (CI 95% 0.63 - 1.23) Based on data from 112 patients in 1 study	**611** per 1000	**538** per 1000	**Very Low** Due to serious risk of bias, Due to serious inconsistency, Due to serious imprecision[8]	We are uncertain whether oral antibiotics increase or decrease hemoptysis
		Difference: **73 fewer** per 1000 (CI 95% 226 fewer - 141 more)			
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
		Difference: **0 fewer** per 1000 (CI 95% 6 fewer - 64 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	**Very Low** Due to serious inconsistency, Due to very serious imprecision[10]	We are uncertain whether oral antibiotics increases or decreases emergence of resistance
		Difference: **0 fewer** per 1000 (CI 95% 0 fewer - 0 fewer)			

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**		
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

1. **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**.
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 oral 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 of 25%, data are consistent with no meaningful difference, appreciable benefit or appreciable harm with oral antibiotics; **Publication bias: No serious**.
4. **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**.
5. **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**.
6. **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**.
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 oral antibiotics.; **Publication bias: No serious**.
8. **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**.
9. **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**.
10. **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. 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		
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	**750** per 1000	**623** per 1000 Difference: **127 fewer** per 1000 (CI 95% 397 fewer - 353 more)	**Very Low** Due to serious risk of bias, Due to serious indirectness, Due to very serious imprecision[1]	We are uncertain whether oral 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 Difference**: 137 fewer** per 1000 (CI 95% 187 fewer - 25 more)	**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
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 Difference: **265 more** per 1000 (CI 95% 30 more - 895 more)	**Low** Due to serious indirectness, Due to serious inconsistency[3]	Oral antibiotics may increase emergence of resistance
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 (CI 95%)	**Low** Due to serious inconsistency, Due to serious imprecision[4]	There were too few deaths, to determine whether continuous oral antibiotics made a difference

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**.
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**.
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**.
4. **Risk of bias: No serious**. **Inconsistency: Serious**. Not applicable - single RCT.; **Indirectness: No serious**. **Imprecision: Serious**. Not assessable. ; **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

3.2.3.3 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. 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 Importance: Critical	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 participants with exacerbations
		Difference: **270 fewer** per 1000 (CI 95% 345 fewer - 165 fewer)			
Hospitalisations Importance: Critical	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
		Difference: **23 fewer** per 1000 (CI 95% 33 fewer - 21 more)			
Emergence of resistance Importance: Critical	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
		Difference: 0 fewer per 1000 (CI 95% 0 fewer - 0 fewer)			
Deaths Importance: Critical	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
		Difference: **0 fewer** per 1000 (CI 95% 0 fewer - 0 fewer)			
Withdrawals (intolerable side effects) Importance: Critical	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
		Difference: **5 more** per 1000 (CI 95% 34 fewer - 115 more)			
Adverse event – diarrhoea Importance: Critical	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
		Difference: **184 more** per 1000 (CI 95% 3 more - 1554 more)			
Adverse event – nausea Importance: Critical	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
		Difference: **38 fewer** per 1000 (CI 95% 82 fewer - 187 more)			
Adverse event – rash Importance: Critical	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
		Difference: **67 more** per 1000 (CI 95% 41 fewer - 368 more)			

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		
Exacerbation rates – continuous Importance: Critical	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

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

3.2.3.4 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. 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 Difference: **120 fewer** per 1000 (CI 95% 249 fewer - 98 more)	**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
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 Difference: **42 fewer** per 1000 (CI 95% 107 fewer - 375 more)	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
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 Difference**: 7 fewer** per 1000 (CI 95% 69 fewer - 90 more)	**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
Emergence of resistance Importance: Critical	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 Difference: **68 more** per 1000 (CI 95% 25 fewer - 556 more)	**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
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	**169** per 1000 Difference: **156 more** per 1000 (CI 95% 3 fewer - 2883 more)	**Low** Due to serious inconsistency, Due to serious imprecision[5]	Nebulised or inhaled antibiotics may have little or no effect on wheeze
Adverse event - dyspnoea Importance: Critical	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 Difference: **243 more** per 1000 (CI 95% 19 more - 974 more)	**Low** Due to serious imprecision, Due to serious inconsistency[6]	Nebulised or inhaled antibiotics may increase dyspnoea
Adverse event - chest pain or palpitations Importance: Critical	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 Difference: **182 more** per 1000 (CI 95% 1 fewer - 3282 more)	**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

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**		
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	**75** per 1000 Difference: **64 fewer** per 1000 (CI 95% 135 fewer - 1323 more)	**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
Adverse event - nausea Importance: Critical	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 Difference: **203 more** per 1000 (CI 95% 11 fewer - 3924 more)	**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
Adverse event - hemoptysis Importance: Critical	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 Difference: **13 more** per 1000 (CI 95% 31 fewer - 155 more)	**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
Adverse event - bronchospasm Importance: Critical	Relative risk 2.01 (CI 95% 0.61 - 6.63) Based on data from 189 patients in 2 studies	**52** per 1000	**105** per 1000 Difference: **53 more** per 1000 (CI 95% 20 fewer - 293 more)	**Very Low** Due to serious risk of bias, Due to very serious imprecision[11]	We are uncertain whether nebulised or 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 Difference: **4 more** per 1000 (CI 95% 8 fewer - 151 more)	**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

1. **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**.
2. **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 I^2: 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**.
3. **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**.
4. **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**.
5. **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**.
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 appreciable harm with inhaled/nebulised antibiotics; **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 benefit/harm with nebulised or inhaled antibiotics; **Publication bias: No serious**.
8. **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**.
9. **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**.
10. **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

3.2.3.5 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 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 (>38ºC), 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) Based on data from 266 patients in 1 study	**886** per 1000	**957** per 1000 Difference: **71 more** per 1000 (CI 95% 0 fewer - 142 more)	**Moderate** Due to serious inconsistency[5]	Aztreonam probably has little or no effect on adverse events
Any adverse event (AIR-BX2) Importance: Critical	Relative risk 1.07 (CI 95% 0.98 - 1.16) Based on data from 272 patients in 1 study	**861** per 1000	**921** per 1000 Difference: **60 more** per 1000 (CI 95% 17 fewer - 138 more)	**Moderate** Due to serious inconsistency[6]	Aztreonam probably has little or no effect on adverse events
Outcome		**Absolute effect estimates**			**Plain text summary**

Timeframe	**Study results and measurements**	**Placebo**	**Aztreonam**	**Certainty in effect estimates** (Quality of evidence)	
Serious adverse event (AIR-BX1) Importance: Critical	Relative risk 2.12 (CI 95% 1.15 - 3.91) Based on data from 266 patients in 1 study	**98** per 1000	**208** per 1000 Difference: **110 more** per 1000 (CI 95% 15 more - 285 more)	**Low** Due to serious inconsistency, Due to serious imprecision[7]	Aztreonam may increase serious adverse events slightly
Serious adverse event (AIR-BX2) Importance: Critical	Relative risk 1.14 (CI 95% 0.61 - 2.14) Based on data from 272 patients in 1 study	**117** per 1000	**133** per 1000 Difference: **16 more** per 1000 (CI 95% 46 fewer - 133 more)	**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
Adverse event leading to study drug discontinuation (AIR-BX1) Importance: Critical	Relative risk 3.69 (CI 95% 1.76 - 7.76) Based on data from 266 patients in 1 study	**61** per 1000	**225** per 1000 Difference: **164 more** per 1000 (CI 95% 46 more - 412 more)	**Moderate** Due to serious inconsistency[9]	Aztreonam probably increases adverse events leading to study drug discontinuation
Adverse events leading to study drug discontinuation (AIR-BX2) Importance: Critical	Relative risk 1.88 (CI 95% 0.78 - 4.58) Based on data from 272 patients in 1 study	**51** per 1000	**96** per 1000 Difference: **45 more** per 1000 (CI 95% 11 fewer - 183 more)	**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
Adverse event - dyspnoea (AIR-BX1) Importance: Critical	Relative risk 1.55 (CI 95% 1.18 - 2.04) Based on data from 266 patients in 1 study	**356** per 1000	**552** per 1000 Difference: **196 more** per 1000 (CI 95% 64 more - 370 more)	**Low** Due to serious inconsistency, Due to serious imprecision[11]	Aztreonam may increase dyspnoea slightly
Adverse event - dyspnoea (AIR-BX2) Importance: Critical	Relative risk 1.08 (CI 95% 0.78 - 1.49) Based on data from 272 patients in 1 study	**343** per 1000	**370** per 1000 Difference: **27 more** per 1000 (CI 95% 75 fewer - 168 more)	**Low** Due to serious inconsistency, Due to serious imprecision[12]	Aztreonam may have little or no effect on dyspnoea

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**.

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4 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 36 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. Seven of the 36 references were prioritised by the committee as the best available evidence and were included in this evidence review (see included studies).

The 29 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 174 references were excluded. These are listed in excluded studies with reasons for their exclusion

See also study flow diagram.

5 Review protocol

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

I	Review question	What pharmacological (antimicrobial and non-antimicrobial) interventions are effective in managing an acute exacerbation of bronchiectasis (non-cystic fibrosis)?	• 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	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: • optimise outcomes for individuals • reduce overuse, misuse or abuse of antimicrobials 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.	The secondary objectives of the review of studies will include: • 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	Population: Adults and children (aged 72 hours and older) with an infective exacerbation of bronchiectasis (non-cystic fibrosis). Studies that use for example symptoms or signs (prognosis), clinical diagnosis, imaging, microbiological methods, or laboratory testing of blood for diagnosing the condition.	Subgroups of interest, those: • 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)	The review will include studies which include: • Non-antimicrobial pharmacological interventions[5]. • Antimicrobial pharmacological interventions[6]. 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).	Limited to those interventions commonly in use (as agreed by the committee)
VI	Eligibility criteria – comparator(s)/ control or reference (gold) standard	Any other plausible strategy or comparator, including: • Placebo or no treatment. • Non-pharmacological interventions. • Non-antimicrobial pharmacological interventions. • Other antimicrobial pharmacological interventions.	

VII	Outcomes and prioritisation	a. Clinical outcomes such as: • 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. a. Thresholds or indications for antimicrobial treatment (which people are most, or least likely to benefit from antimicrobials) b. Changes in antimicrobial resistance patterns, trends and levels as a result of treatment. c. Patient-reported outcomes, such as medicines adherence, patient experience and patient satisfaction. d. Ability to carry out activities of daily living. e. Service user experience. f. Health and social care related quality of life, including long-term harm or disability. g. Health and social care utilisation (including length of stay, planned and unplanned contacts). 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 condition (for example length of study follow-up, treatment failure/recurrence, important outcomes of interest such as sequela or progression to more severe illness).	The committee have agreed that the following outcomes are critical: • 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 for example C-reactive protein, procalcitonin) The committee have agreed that the following outcomes are important: • patient-reported outcomes, such as medicines adherence, patient experience, sickness absence • changes in antimicrobial resistance patterns, trends and levels as a result of treatment

VIII	Eligibility criteria – study design	The search will look for: • Systematic review of randomised controlled trials (RCTs) • RCTs If insufficient evidence is available progress to: • 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	The scope sets out what the guidelines will and will not include (exclusions). Further exclusions specific to this guideline include: • 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	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.	

XI	Selection process – duplicate screening/ selection/ analysis	All references from the database searches will be downloaded, de-duplicated and screened on title and abstract against the criteria above. 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 screened by one reviewer only. Disagreement will be resolved through discussion. Where abstracts meet all the criteria, or if it is unclear from the study abstract whether it does, the full text will be retrieved. 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.	
XII	Data management (software)	Data management will be undertaken using EPPI-reviewer software. GRADEpro will be used to assess the quality of evidence for each outcome.	

XIII	Information sources – databases and dates	The following sources will be searched: • 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 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. Database functionality will be used, where available, to exclude: • non-English language papers • animal studies • editorials, letters, news items, case reports and commentaries • conference abstracts and posters • theses and dissertations • duplicates. Date limits will be applied to restrict the search results to: • studies published from 2006 to the present day The results will be downloaded in the following mutually exclusive sets: • Systematic reviews and meta-analysis • Randomised controlled trials • Observational and comparative studies • Other results See appendix B for further details on the search strategy. Duplicates will be removed using automated and manual processes. The de-duplicated file will be uploaded into EPPI-Reviewer for data screening.	

XV	Author contacts	Web: https://www.nice.org.uk/guidance/indevelopment/gid-ng10050/consultation/html-content Email: infections@nice.org.uk	
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 at outcome/ study level	Standard study checklists were used to critically appraise individual studies. For details please see the interim process 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.	
XXVIII	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.	

[1] significant heart, lung, renal, liver or neuromuscular disease, immunosuppression, and young children who were born prematurely

[2] Including pneumonia, heart, lung, kidney, liver or neuromuscular disease, or immunosuppression

[3] Outlined in more detail in CG160 Fever in under 5s: assessment and initial management

[4] hospitalisation in previous year; type 1 or type 2 diabetes, history of congestive heart failure, current use of oral glucocorticoids.

[5] Non-antimicrobial pharmacological interventions include: analgesics and bronchodilators

[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

[7] These would include but are not limited to more common complications e.g. chronic bacterial colonization and haemoptysis

6 Evidence prioritisation

Key questions	Included studies		Non-prioritised studies	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Which non-pharmacological interventions are effective?				
Non-pharmacological interventions	-	-	-	-
Which non-antimicrobial pharmacological interventions are effective?				
Mucoactives	Wilkinson et al. 2014 Hart et al. 2014	-	Magis-Escurra et al. 2015 Tarrant et al. 2017	Kellett et al. 2011 Bilton et al. 2013 Bilton et al. 2014
Inhaled corticosteroids	Kapur et al. 2009	-	Magis-Escurra et al. 2015	Martinez-Garcia et al. 2006 Hernando et al. 2012
Inhaled corticosteroid plus long-acting beta2 agonists	Goyal et al. 2014	-	-	Martinez-Garcia et al. 2012
Which antibiotic prescribing strategies are effective (including back-up antibiotics)?				
Antibiotic prescribing strategies	-	-	-	-

Key questions	Included studies		Non-prioritised studies	
	Systematic reviews	RCTs	Systematic reviews	RCTs
Is an antibiotic effective?				
Prolonged antibiotics versus placebo	Hnin et al. 2015 Barker et al. 2014	-	Fan et al. 2015 Gao et al. 2014 Wu et al. 2014 Zhuo et al. 2014 Magis-Escurra et al. 2015 Brodt 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 Antoniu 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	-	-	-	-

7 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
	Fosfomycin	Fosfomycin/ (Fosfomycin* 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 Vancomicin* 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

Main concepts	Concept	Proposed search terms
	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/ 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 Pizotyline* 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

Main concepts	Concept	Proposed search terms
	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
	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.

Main concepts	Concept	Proposed search terms
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 No intervention Watchful waiting	watchful waiting/ "no intervention*".ti,ab (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	((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 ((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 ((delay* or defer*) adj3 (treat* or therap* or interven*)).ti,ab. anti-infective agents/ or exp anti-bacterial agents/ or exp anti-infective agents, local/ (antibacter* or anti-bacter* or antibiot* or anti-biot* or antimicrobial* or anti-microbial*).ti,ab. (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 Inappropriate prescribing/
Self Care	Self management	Self Care/ Self medication/ ((self or selves or themsel*) adj4 (care or manag*)).ti,ab
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
3	((suppurative* or dilat*) adj3 (pulmonary or lung* or airway* or airflow* or bronch* or respirat*)).ti,ab.	4250

#	Searches	Results
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
37	Cefuroxime/	2190
38	(Cefuroxime* or Cephuroxime* or Zinacef* or Zinnat* or Aprokam*).ti,ab.	4252

#	Searches	Results
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
69	(Levofloxacin* or Evoxil* or Tavanic*).ti,ab.	6630
70	Linezolid/	2602

#	Searches	Results
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
104	exp Polymyxins/	8642
105	Polymyxin*.ti,ab.	6754
106	exp Quinolones/	45049

#	Searches	Results
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
136	exp Histamine Antagonists/	63384
137	Antazoline/	212
138	Brompheniramine/	351

#	Searches	Results
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	Triprolidine/	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 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 Pizotyline* or Triprolidine* 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
167	Dextromethorphan*.ti,ab.	2510
168	Leukotriene Antagonists/	3063
169	(leukotriene* adj3 (antagonist* or agonist* or agent* or inhibitor* or blocker*)).ti,ab.	3803

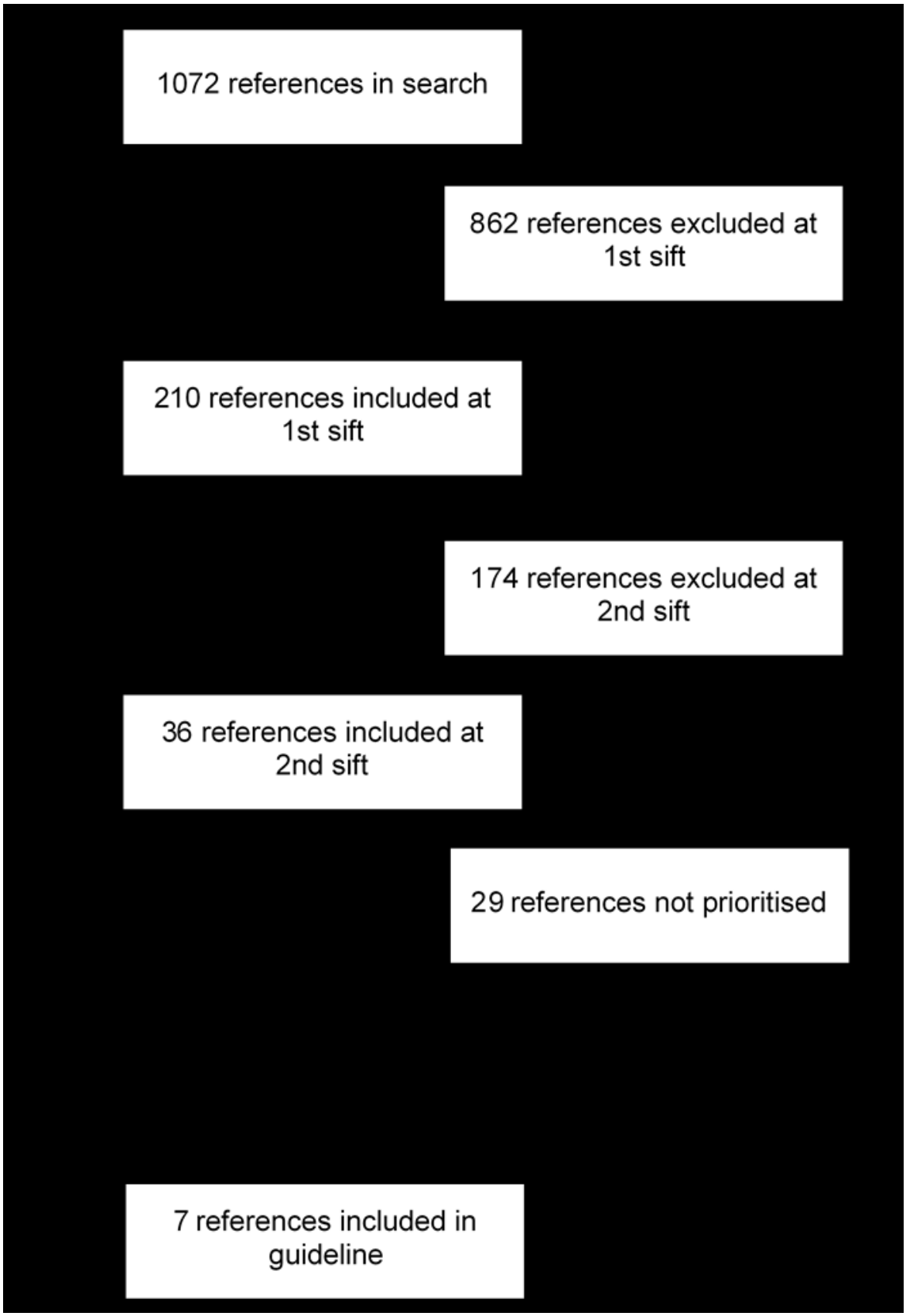
#	Searches	Results
170	Montelukast*.ti,ab.	1981
171	(Zafirlukast* or Accolate*).ti,ab.	419
172	exp Expectorants/	16613
173	exp Guaifenesin/	778
174	Ipecac/	639
175	(expectorant* or mucolytic* or guaifenesin* or ipecac* or ipecacuanha*).ti,ab.	3104
176	Mannitol/	12727
177	(Mannitol* or Osmohale* or Bronchitol*).ti,ab.	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
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

#	Searches	Results
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
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

#	Searches	Results
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
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

#	Searches	Results
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

8 Study flow diagram



9 Included studies

9.1 References

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

Comments:

Risk of bias assessment using the CASP Tool

Study reference	Wilkinson 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?	Yes
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

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

Comments:

Risk of bias assessment using the CASP Tool

Study reference	Hart 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?	Yes
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

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

Comments:

Risk of bias assessment using the CASP Tool

Study reference	Goyal 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?	Yes
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

Kapur Nitin, Bell Scott, Kolbe John, and Chang Anne B (2009) Inhaled steroids for bronchiectasis. The Cochrane database of systematic reviews (1), CD000996

Comments:

Risk of bias assessment using the CASP Tool

Study reference	Kapur et al. 2009
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?	Yes
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

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

10 Studies not prioritised

Study reference	Reason
Brodt 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
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	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

Study reference	Reason
Antoniu 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
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	RCT included in a systematic review that has been prioritised
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	RCT included in a systematic review that has been prioritised
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
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	Systematic review has been prioritised
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	RCT included in a systematic review that has been prioritised
Lourdesamy Anthony, Albert I, and Muthukumaru Umadevi (2014) Efficacy of azithromycin in the treatment of bronchiectasis. Respirology (Carlton, and Vic.) 19(8), 1178-82	Systematic review has been prioritised
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	RCT included in a systematic review that has been prioritised
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	RCT included in a systematic review that 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

Study reference	Reason
Orriols Ramon, Hernando Rosana, Ferrer Adelaida, Terradas Sonia, and Montoro Bruno (2015) Eradication Therapy against *Pseudomonas aeruginosa* 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
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. The Lancet. Respiratory medicine 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. Lancet (London, and England) 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. Journal of clinical pharmacy and therapeutics 31(1), 49-55	RCT included in a systematic review that has been prioritised

11 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. Current opinion in pulmonary medicine 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. Contemporary clinical trials 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 Kl, 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). 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)
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. Journal of the American Geriatrics Society 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. Journal of the American Geriatrics Society 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. European respiratory journal 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. The Netherlands journal of medicine 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 Jl (2016) Antibiotics for preventing suppurative complications from undifferentiated acute respiratory infections in children under five years of age. Cochrane Database of Systematic Reviews (2),	Not relevant population
Amorim A, Gamboa F, and Azevedo P (2013) New advances in the therapy of non-cystic fibrosis bronchiectasis. Revista portuguesa de pneumologia 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. Respiratory Care 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-fi brosis 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 *Pseudomonas aeruginosa*. 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, McKevitt 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 *Pseudomonas aeruginosa*. 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 *Pseudomonas aeruginosa* 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 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 *Pseudomonas aeruginosa* 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
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

Study reference	Reason for exclusion
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)
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)

Study reference	Reason for exclusion
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, Melachroinidou M, Gousiou A, and Toumbis M (2017) Non cf bronchiectasis: the effect of inhaled antibiotics (tobramycin and colistin) in patients with *Pseudomonas aeruginosa* 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 *Pseudomonas aeruginosa*. European respiratory journal 44,	Publication/ study type (abstract only)
Ding H, Wang J-G, Sun X-Y, and Xu L-J (2006) Responsibility to bronchodilatator 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)
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)

Study reference	Reason for exclusion
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)
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 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)

Study reference	Reason for exclusion
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 VRP1 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
Haworth C, Bilton D, and Kenyon R (2013) Nebulised colistimethate sodium improves quality of life in patients with bronchiectasis colonised by *Pseudomonas aeruginosa*. 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 *Pseudomonas aeruginosa* 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 *Pseudomonas aeruginosa* 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)
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	Not relevant population
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)

Study reference	Reason for exclusion
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
Ilowite Jonathan, Spiegler Peter, and Chawla Shalinee (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-inflammatoy 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 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)
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)

Study reference	Reason for exclusion
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)
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 etal.: 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)

Study reference	Reason for exclusion
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)
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)

Study reference	Reason for exclusion
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 *Pseudomonas aeruginosa* (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
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)

Study reference	Reason for exclusion
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 Kl, 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)
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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
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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)
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)

Study reference	Reason for exclusion
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Serisier Dj, Thompson Pj, Greville H, Kolbe J, and Bruinenberg Pr (2011) Dual release ciprofloxacin for inhalation (DRCFI) reduces sputum *Pseudomonas aeruginosa* (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)
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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
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)
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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 Jl, 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)
Tabernero Huguet E; Gil Alaña P; Alkiza Basañez R; Hernández Gil A; Garros Garay J; Artola Igarza Jl; (2015) Inhaled colistin in elderly patients with non-cystic fibrosis bronchiectasis and chronic *Pseudomonas aeruginosa* bronchial infection. Revista espanola de geriatria y gerontologia 50(3), 111-115	Publication/ study type (abstract only)

Study reference	Reason for exclusion
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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)
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 MeetingAbstracts),	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)

Study reference	Reason for exclusion
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)

12 Terms used in this guideline

12.1 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 a worsening cough (with increased sputum volume, viscosity, or purulence) with or without increased wheeze, breathlessness or haemoptysis; and/or fever or pleurisy. The presence of mucopurulent or purulent sputum alone without a deterioration in symptoms is not necessarily an acute exacerbation (NICE clinical knowledge summary – bronchiectasis, British Thoracic Society guideline on non-cystic fibrosis bronchiectasis 2010).