Non-cystic fibrosis bronchiectasis: inhaled tobramycin

Evidence summary
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Key points

The content of this evidence summary was up-to-date in April 2017. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Regulatory status: Tobramycin is an aminoglycoside antibiotic. Inhaled (nebuliser solution and inhalation powder) preparations, TOBI, Bramitob, Vantobra and TOBI podhaler are licensed for the management of chronic pulmonary infection caused by Pseudomonas aeruginosa in patients with cystic fibrosis aged 6 years and older. Use of inhaled tobramycin for treating infective exacerbations caused by Pseudomonas aeruginosa in non-cystic fibrosis bronchiectasis is off-label.

Overview

This evidence summary includes 3 randomised controlled trials that investigated the efficacy of nebulised tobramycin, 300 mg twice daily compared with placebo for treating infective exacerbations caused by P aeruginosa in people with non-cystic fibrosis bronchiectasis. The treatment duration varied across the studies from 4 weeks to 6 months.

Compared with placebo, statistically significant reductions were seen with 4 weeks to 6 months treatment with nebulised tobramycin in:

- sputum P aeruginosa density (1 study)
Compared with placebo, no statistically significant improvements were seen with nebulised tobramycin in:

- pulmonary function (forced expiratory volume at 1 second [FEV₁] and forced vital capacity [FVC]; 3 studies)
- quality of life (St George's respiratory questionnaire; 2 studies).

Of the 2 studies that reported number of exacerbations as an outcome, when compared with placebo, 1 study found no statistically significant reduction in the number of exacerbations per person over 6 months treatment with tobramycin, and 1 study found a statistically significant reduction in the number of exacerbations over 3 months of treatment with tobramycin. One study found that more participants in the tobramycin group were classified by the investigators as having improved medical condition compared with placebo. However, this finding was limited as it was based on a subjective assessment that did not use a validated tool.

The studies included in the evidence summary had many limitations that affect their application to clinical practice. All studies included small numbers of participants (n=30 to 74) in the US or Spain. The study populations varied and it is unclear which patients might benefit most from treatment and for how long to treat infective exacerbations caused by *P aeruginosa* in people with non-cystic fibrosis bronchiectasis.

The adverse events seen in the studies reflect those listed in the SPC for TOBI (nebuliser solution). These include dyspnoea, chest pain, cough and bronchospasm.

The improvement in some of the reported outcomes in the studies must be balanced with the risk of experiencing adverse effects and the development of bacterial resistance. In current practice, when nebulised treatment is indicated for *P aeruginosa* infections in people with non-cystic fibrosis bronchiectasis, inhaled tobramycin is considered when treatment with other commonly used nebulised therapies is not tolerated, if the condition is deteriorating while on other nebulised antibiotics, or if cultures are sensitive to tobramycin.

A summary to inform local decision-making is shown in table 1.

**Table 1 Summary of the evidence on effectiveness, safety, patient factors and resource implications**
Effectiveness

- At 12-month follow-up, Orriols et al. (2015) (n=35) found that 3 months' treatment with nebulised tobramycin showed a statistically significant reduction in the number of exacerbations compared with placebo (p=0.04).

- Drobnic et al. (2005) (n=30) reported a statistically significant reduction in the number of hospital admissions with tobramycin compared with placebo (p=0.038). Orriols et al. (2015) also found a statistically significant reduction in the same outcome (p=0.04).

- Drobnic et al. (2005) reported a statistically significant reduction in the number of days in hospital with tobramycin compared with placebo (p=0.047). Orriols et al. (2015) also found a statistically significant reduction in the same outcome (p=0.03).

- After 4 weeks' treatment, Barker et al. (2000) (n=74) found a statistical significant mean decrease in sputum *P aeruginosa* density in the tobramycin group compared with placebo (p<0.01).

- The optimal duration of treatment with inhaled tobramycin for treating non-cystic fibrosis bronchiectasis exacerbations caused by *P aeruginosa* has not been established. The risk of contributing to the emergence of bacterial resistance needs to be considered with prolonged antibiotic therapy.
Safety

- According to the SPC for TOBI (nebuliser solution), very common adverse effects (incidence 1 in 10 or more) include lung disorder, rhinitis, dysphonia (difficulty in speaking), discoloured sputum and decreased pulmonary function test. Common adverse effects (incidence between 1 in 100 and 10 in 100) include laryngitis, tinnitus, myalgia and malaise.

- The incidence of adverse effects varies between the different inhaled tobramycin preparations, see individual SPCs for Bramitob, Vantobra and TOBI podhaler for further information.

- Four deaths in people using tobramycin and 1 death in a person using placebo caused by respiratory failure were reported during the studies, however it was not clear if the deaths were considered to be related to the study medication.

- Eleven withdrawals caused by adverse effects were reported with tobramycin in the studies (mainly because of bronchospasm) compared with 2 withdrawals in the placebo groups.

- Most common adverse effects reported in the studies included bronchospasm, cough, dyspnoea, chest pain, wheezing, haemoptysis and mild transient tinnitus.

Patient factors

- Current clinical practice suggests baseline renal function should be assessed and urea and creatinine levels should be reassessed after every 6 complete cycles of inhaled tobramycin therapy (180 days total of aminoglycoside therapy; SPC: TOBI [nebuliser solution]).

- The first dose of tobramycin should be given under medical supervision because bronchospasm can occur following inhalation of tobramycin and has been reported with inhaled preparations (SPC: TOBI [nebuliser solution]).

- Some people may find it difficult or inconvenient to use a nebuliser.

- Inhalation of nebulised solutions may induce a cough reflex (SPC: TOBI [nebuliser solution]).

- The included studies did not investigate the efficacy and safety of inhaled tobramycin in children.
Resource implications

- Two of the 3 studies in this evidence summary used the TOBI brand of tobramycin nebuliser solution. Costs for 28 days’ treatment for TOBI at a dose of 300 mg twice daily as used in the studies would be £1,305.92 ([Drug Tariff; March 2017]).

- Bramitob and Vantobra nebuliser solutions are also available in the UK; 28-day treatment costs for them based on the dose used for their licensed indications would be; £1,187.00, and £1,305.00 respectively ([MIMS; March 2017]).

- One of the 3 studies in this evidence summary used tobramycin solution for injection as a nebulised therapy at a dose of 300 mg twice daily. However, specialists involved in the production of this evidence summary suggested that when the injection is used as a nebulised therapy, a dose of 80 mg to 160 mg twice a day is used in practice. Costs of 28 days’ treatment using this preparation at a dose of 80 mg to 160 mg twice daily would cost £211.12 to £422.24 ([BNF; March 2017]).

- These costs are for the medicine only and do not include VAT, any local procurement discounts or other costs incurred, such as dilution and administration or standard supportive therapy.

- The acquisition cost of nebulised tobramycin is more than that of other inhaled antibiotics that are recommended by the [British Thoracic Society](https://www.brit-thoracic.org.uk/) for non-cystic fibrosis bronchiectasis.

Introduction and current guidance

Bronchiectasis is a permanent dilatation and thickening of the airways associated with chronic cough, sputum production, bacterial colonisation, and recurrent infection. It is associated with a wide range of diseases (for example, previous lower respiratory tract infection, immune deficiency, congenital airway abnormality, allergic bronchopulmonary aspergillosis, and aspiration injury) but often the cause is unknown. Bronchiectasis can present at any age but the prevalence increases with age and the highest prevalence is in older women ([O’Donnell 2008](https://www.ncbi.nlm.nih.gov/pubmed/18915089)). It is estimated that around 1,000 people die each year from bronchiectasis in England and Wales ([Roberts and Hubbard 2010](https://www.ncbi.nlm.nih.gov/pubmed/20340869)).

The prognosis for bronchiectasis varies widely. Most people have intermittent lower respiratory tract infections but otherwise few or no symptoms and a normal life expectancy. More severe disease results in daily symptoms, progressive loss of lung function, and a reduced life expectancy.
The prognosis is worse if the person smokes, has extensive disease or frequent exacerbations, or if their lungs are colonised by *P aeruginosa* (NICE clinical knowledge summary: bronchiectasis).

NICE has not published a guideline on non-cystic fibrosis bronchiectasis. According to the British Thoracic Society (BTS) guideline for non-cystic fibrosis bronchiectasis (being updated, likely publication date 2017), which has been accredited by NICE, treatments for non-cystic fibrosis bronchiectasis include airway clearance using physiotherapy, pulmonary rehabilitation, antibiotics, bronchodilators (beta-2 agonists and anticholinergics) and surgery. The overall aim of treatment in people with non-cystic fibrosis bronchiectasis is to reduce symptoms, maintain lung function and prevent exacerbations thereby improving quality of life and long-term outcomes (BTS guideline for non-cystic fibrosis bronchiectasis). The guideline recommends that antibiotic courses should be given for exacerbations that present with an acute deterioration and worsening symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness or haemoptysis) or systemic illness. Sputum culture is recommended to determine which antibiotic should be used when indicated.

The BTS guideline recommends considering long-term oral or nebulised antibiotics for people with non-cystic fibrosis bronchiectasis who have 3 or more exacerbations per year that need antibiotic therapy, or in people who have fewer exacerbations but that are causing significant morbidity. Long-term nebulised antibiotics (gentamicin, tobramycin and colistimethate sodium) should be considered in people who have chronic *P aeruginosa* infection, with the choice of antibiotic guided by the results of tests for antibiotic sensitivity. The BTS guideline states that further studies are needed to identify the optimal antibiotic choice and doses.

Since the BTS guideline for non-cystic fibrosis bronchiectasis was published in 2010, randomised controlled trials on the use of tobramycin for this condition have been published. This evidence summary considers the evidence for the safety and efficacy of inhaled (includes nebuliser solution and inhalation powder) tobramycin in treating infective exacerbations caused by *P aeruginosa* in people with non-cystic fibrosis bronchiectasis.

**Product overview**

**Mode of action**

Tobramycin is an aminoglycoside antibiotic. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death (summary of product characteristics [SPC]: TOBI [nebuliser solution]).
Inhaled tobramycin is used in people with cystic fibrosis infected with *P. aeruginosa*. Compared with oral and intravenous administration, inhaled administration of an antibiotic can deliver high concentrations directly to the site of infection, eliminating the need for high systemic concentrations and reducing the risk of systemic toxicity (Barker et al. 2000).

**Regulatory status**

Tobramycin nebuliser solutions (Bramitob, TOBI [nebuliser solution] and Vantobra) and an inhalation powder (TOBI podhaler) are licensed for treating chronic pulmonary infections caused by *P. aeruginosa* in people with cystic fibrosis aged 6 years or older.

Use of inhaled tobramycin for treating infections in non-cystic fibrosis bronchiectasis is off-label.

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the patient and whether using tobramycin is suitable outside its authorised indications. Supporting information and advice is also available from the GMC.

**Dosing information**

Dosing information for inhaled tobramycin varies depending on the preparation. The recommended nebulised dose for its licensed indication for chronic pulmonary infection due to *P. aeruginosa* in people with cystic fibrosis is 300 mg twice daily (Bramitob and TOBI [nebuliser solution]) or 170 mg twice daily (Vantobra). The recommended inhaled dose for the same licensed indication when using the TOBI podhaler is 112 mg twice daily. The SPCs for Bramitob, TOBI nebuliser solution, Vantobra and TOBI podhaler state that a cycle of 28 days of active therapy and 28 days of rest from treatment should be maintained. See individual summary of product characteristics for further dosing information.

Dosing information for inhaled tobramycin for non-cystic fibrosis bronchiectasis (an off-label indication) is discussed in the evidence review.

**Cost**

The costs of tobramycin preparations (excluding VAT; NHS indicative prices) are:

- £1187.00 for 56×4 ml ampoules for Bramitob 300 mg/4 ml nebuliser solution (MIMS; March 2017)
- £1305.92 for 56×5 ml ampoules for TOBI 300 mg/5 ml nebuliser solution (Drug Tariff; March 2017)

- £1305.00 for 56×1.7 ml ampoules for Vantobra 170 mg/1.7 ml nebuliser solution (MIMS; March 2017)

- £447.50 for 56 capsules each containing 28 mg of tobramycin plus 1 podhaler device for TOBI podhaler (MIMS; March 2017)

- £3.70, £3.77 and £45.00 for 1 vial containing 40 mg (1 ml), 80 mg (2 ml) and 240 mg (6 ml) respectively of tobramycin 40 mg/ml solution for injection (BNF; March 2017).

Evidence review

A literature search was conducted which identified 123 references (see search strategy for full details). These references were screened using their titles and abstracts and 19 references were obtained and assessed for relevance.

Three randomised controlled trials (RCTs) identified from the search (Barker et al. 2000, Drobnic et al. 2005 and Orriols et al. 2015) were included in this evidence summary. A summary of the included studies is shown in table 2 (see evidence tables for full details). The included studies were carried out in adult populations. There were no studies identified in children with non-cystic fibrosis bronchiectasis.

The remaining 16 references were excluded. These are listed in excluded studies with reasons for their exclusion.

Table 2 Summary of included studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Intervention and comparison</th>
<th>Primary outcomes unless stated otherwise</th>
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<tbody>
<tr>
<td>Barker et al. 2000</td>
<td>Adults with non-CF bronchiectasis producing purulent sputum containing <em>P. aeruginosa</em> n=74</td>
<td>TSI 300 mg twice daily versus placebo for 4 weeks</td>
<td>- Change in <em>P. aeruginosa</em> density from baseline to end of treatment</td>
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</table>
Clinical effectiveness

This evidence summary is based on 3 RCTs that assessed the efficacy of inhaled tobramycin for treating non-cystic fibrosis bronchiectasis in adults (mean age in the studies ranged from 63.2 to 70.1 years).

Exacerbations and number of hospital admissions

Respiratory exacerbations were reported as a primary outcome by Drobnic et al. (2005). Orriols et al. (2015) also reported number of exacerbations as an outcome but it was not clear if it was a primary outcome in the study. In both studies supplementary use of oral antibiotics was allowed to treat exacerbations. The participants in both studies completed 2 weeks of intravenous treatment with ceftazidime and tobramycin before receiving nebulised tobramycin. This same regimen was used to treat exacerbations that required hospital admission in the study by Drobnic et al. (2005). Orriols et al. (2015) did not report which antibiotics were used to treat exacerbations.

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>Outcomes</th>
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| Drobnic et al. 2005 (RCT crossover) | Adults with non-CF bronchiectasis producing purulent sputum containing *P. aeruginosa* n=30 | Nebulised tobramycin (IV preparation used) 300 mg twice daily versus placebo for 6 months, crossover study | • Number of exacerbations  
• Number and days of hospital admissions |
| Orriols et al. 2015 (RCT) | Adults with non-CF bronchiectasis producing purulent sputum containing *P. aeruginosa* n=35 | TSI 300 mg twice daily versus placebo for 3 months | Primary and secondary outcomes were not clearly defined in the study but included the following:  
• Eradication rate of *P. aeruginosa*  
• Number of exacerbations  
• Number and days of hospital admissions |

**Abbreviations:** CF, cystic fibrosis; IV, intravenous; RCT, randomised controlled trial; TSI, tobramycin solution for inhalation.
At 6-month follow-up, Drobnic et al. (2005; n=30) found no statistically significant difference in the mean number of respiratory exacerbations per person between the tobramycin and the placebo periods \((p=0.330)\). However, the mean number of exacerbations that required admission and the mean number of days of hospital admissions per person were significantly lower in the tobramycin period than in the placebo period (0.15 versus 0.75, \(p=0.038\) and 2.05 versus 12.65, \(p=0.047\) respectively).

At 12-month follow-up, Orriols et al. (2015) (n=35) found that tobramycin compared with placebo significantly reduced the mean number of exacerbations (1.27 versus 2.5, \(p=0.04\)), mean number of admissions (0.06 versus 0.47, \(p=0.03\)) and mean number of days of hospital admission in (0.90 versus 13.567, \(p=0.04\)).

In the study by Barker et al. (2000), the number of exacerbations was not included as an outcome, however the authors reported that 5 of the participants in the tobramycin group and 1 participant in the placebo group were admitted to hospital and treated for exacerbation of their bronchiectasis with additional antibiotics.

**Lung function**

All 3 studies (Barker et al. 2000, Drobnic et al. 2005 and Orriols et al. 2015) reported lung function as an outcome (reported as secondary outcomes by Barker et al. 2000 and Drobnic et al. 2005; Orriols et al. 2015 did not state if this was a primary or secondary outcome) that was measured by using the forced expiratory volume in 1 second (FEV\(_1\)) and forced vital capacity (FVC). No significant difference was observed between the tobramycin and placebo groups in all 3 studies for this outcome.

**Improvement in medical condition and health-related quality of life**

Barker et al. (2000) reported the changes in the participant’s general medical condition (reported as ‘improved’ or ‘not improved’). This was reported using the investigator’s subjective assessment at week 6 of the study period. Barker et al. (2000) reported that 62% (23/37) of participants in the tobramycin group compared with 38% (14/37) in the placebo group were assessed as having an improved medical condition (odds ratio [OR] 2.7, 95% confidence interval [CI] 1.1 to 6.9, p value not reported) by the investigator. More females than males were assessed as improved (62% and 31% respectively, \(p=0.01\)).

Drobnic et al. (2005) and Orriols et al. (2015) found that there was no significant improvement in participants’ health-related quality of life assessed using St George’s respiratory questionnaire (SGRQ) for either tobramycin or placebo. In the study by Drobnic et al. (2005), the mean change
from baseline to the end of treatment in the SGRQ total scores in both tobramycin and placebo periods was −0.90 and −0.83 (p=0.97). The change in scores for symptoms, activity and impact were also found to be similar between tobramycin and placebo with no statistically significant difference. Orriols et al. (2015) found that the mean change in the total SGRQ scores for tobramycin and placebo was −14.6 and −4.9 (p=0.31) and a non-statistical significant difference between tobramycin and placebo for the change in individual component scores.

**Bacterial density, eradication and recurrence**

All 3 studies reported similar findings for these outcomes. Tobramycin was found to decrease sputum *P. aeruginosa* density during the treatment periods compared with little or no change seen in the placebo group. However after stopping tobramycin treatment, regrowth or recurrence was observed in all 3 studies.

*Barker et al. (2000)* found a statistically significant mean decrease in sputum *P. aeruginosa* density in the tobramycin group compared with negligible or no changes observed in the placebo group (p<0.01 at week 4). At week 6, Barker et al. (2000) reported a smaller mean decrease in *P. aeruginosa* density in the tobramycin group indicating recurrence after stopping tobramycin treatment. Barker et al. (2000) found *P. aeruginosa* was eradicated in 35% (n=13) with tobramycin compared with no participants receiving placebo.

*Drobnic et al. (2005)* found a statistically significant decrease in *P. aeruginosa* density in sputum in participants during the tobramycin period in the first 6 months of the cycle (p=0.038). Eradication of *P. aeruginosa* was observed in 4 participants during the tobramycin period and 4 participants during the placebo period. The study also reported that disappearance of *P. aeruginosa* in culture was transient and regrowth was observed after a mean time of 3 months.

*Orriols et al. (2015)* found a higher proportion of participants in the tobramycin group were free of *P. aeruginosa* than in the placebo group in the first month, 90% and 76.5% respectively. However, at 12-month follow-up, the proportion of participants free of *P. aeruginosa* were 54.5% and 29.4% in the tobramycin and placebo groups respectively. The median time to recurrence of *P. aeruginosa* infection was significantly higher in the tobramycin than in the placebo group (p=0.048).

**Other outcomes**

There was no statistically significant difference in the emergence of bacterial resistance between tobramycin and placebo groups in the 3 studies. *Barker et al. (2000)* found that 11% (4/36) of participants in the tobramycin group and 3% (1/32) of participants in the placebo group who began the study with susceptible *P. aeruginosa* developed resistant *P. aeruginosa* at week 6 (p=0.36).
Drobnic et al. (2005) found resistant *P. aeruginosa* in the sputum of 2 participants during the tobramycin period that persisted until months 2 and 3 of the placebo period. Resistant *P. aeruginosa* in the sputum of 2 other participants was isolated in the placebo period. Drobnic et al. (2005) also found no significant difference between tobramycin and placebo periods in the frequency of emergence of resistant strains. Orriols et al. (2015) found no tobramycin-resistant *P. aeruginosa* during the study.

In Drobnic et al. (2005) and Orriols et al. (2015), the number of days of additional antibiotic use during the studies was longer with placebo (19 days) compared with tobramycin (8 days), however this difference was not statistically significant (p=0.052).

An overview of the results for clinical effectiveness can be found in results tables.

**Safety and tolerability**

Two of the studies included in the evidence review used the TOBI preparation of tobramycin nebuliser solution as the intervention. The summary of product characteristics (SPC) for TOBI nebuliser solution states that it should be used with caution in people with known or suspected renal, auditory, vestibular or neuromuscular dysfunction, or with severe, active haemoptysis. The first dose of tobramycin should be given under medical supervision because bronchospasm can occur.

Serum tobramycin concentrations should be monitored in people with known or suspected auditory or renal dysfunction, and in people who are receiving concomitant parenteral aminoglycoside therapy. Audiological assessment should be considered in people with a predisposing risk of ototoxicity due to previous prolonged systemic aminoglycoside therapy before starting nebulised or inhaled therapy. Current clinical practice suggests baseline renal function should be assessed and urea and creatinine levels should be reassessed after every 6 complete cycles of inhaled tobramycin therapy (180 days total of nebulised aminoglycoside therapy; SPC: TOBI [nebuliser solution]).

According to the SPC for TOBI (nebuliser solution), very common adverse effects (incidence 1 in 10 or more) include lung disorder, rhinitis, dysphonia (difficulty in speaking), discoloured sputum and decreased pulmonary function test. Common adverse effects (incidence between 1 in 100 and 10 in 100) include laryngitis, tinnitus, myalgia and malaise. The SPCs for other inhaled tobramycin preparations report additional or different adverse effects to those reported in the SPC for TOBI (nebuliser solution) and the incidence of adverse effects varies between the different preparations. See individual SPCs for Bramitob, Vantobra and TOBI podhaler for further details.
In Barker et al. (2000), respiratory adverse events were reported by 70% (26/37) of participants in the tobramycin group and by 51% (19/37) of participants in the placebo group. No significant differences were found between the groups in the number of people reporting at least 1 adverse event. However, there was a statistically significant difference between tobramycin and placebo in the number of people reporting respiratory system adverse events. Tobramycin treated participants reported more dyspnoea (32% compared with 8%), chest pain (19% compared with 0%) and wheezing (16% compared with 0%) than people in the placebo group (p=0.01 for all 3 comparisons). For participants who experienced adverse events, the investigators in the study reported that the adverse events were related to tobramycin treatment in 80% (12/15) of those reporting cough, 25% (3/12) of those reporting dyspnoea, 50% (3/6) of those reporting wheezing and 43% (3/7) of those reporting chest pain. The number of participants withdrawing from the study due to adverse events was 8% (3/37) and 5% (2/37) in the tobramycin and placebo groups. The proportion of participants who withdrew because they used antibiotics other than the study medicine was 5% (2/37) and 16% (6/37) in the tobramycin and placebo groups respectively. One participant in the tobramycin group was lost at follow-up. No clinically significant changes in laboratory values including blood urea nitrogen and creatinine were found between the tobramycin and placebo groups.

In the study by Drobnic et al. (2005), an intravenous preparation of tobramycin was used as a nebulised treatment twice daily for 6 months. Bronchospasm was reported in 10% (n=3/30) of participants during the tobramycin period and all withdrew from the study. Five participants died from respiratory failure, 4 during the tobramycin period and 1 during the placebo period. The authors report that these participants had worse baseline pulmonary function than the 20 participants who completed the study. Drobnic et al. (2005) suggest that deteriorating lung function might be a predictive factor of mortality in people with chronic bronchiectasis and it may be possible that people with impaired lung function may have a different response to inhaled treatment. The fact that 4 of the participants were receiving tobramycin may suggest that tobramycin was the determining factor in the cause of death (Drobnic et al. 2005). The authors also report that tobramycin was generally well tolerated by 20 participants who completed the study. Minor haemoptysis was reported during both study periods by 1 participant and mild transient tinnitus was reported by 1 participant during the tobramycin period. No changes were observed in auditory acuity and serum creatinine concentration during the study.

In the study by Orriols et al. (2015), 5 participants in the tobramycin group withdrew from the study due to bronchospasm during the first month of treatment and these participants were found to have a worse FEV1 at the start of the study (p=0.052) compared with the other remaining participants. No auditory acuity changes were found in either group and serum creatinine concentrations remained within the normal range throughout the study period in all participants.
An overview of the results for safety and tolerability can be found in results tables.

Evidence strengths and limitations

The 3 studies included in this evidence review were randomised controlled studies comparing inhaled tobramycin with placebo. There was no active comparator which would have been useful to compare the efficacy and safety profile of tobramycin with other inhaled antibiotics used in practice for treating infective exacerbations caused by *P aeruginosa* in people with non-cystic fibrosis bronchiectasis.

Barker et al. (2000) and Orriols et al. (2015) reported on the randomisation methods used in their studies, however, Drobnic et al. (2005) did not. All 3 studies had a lack of information about allocation concealment which raises concerns about selection bias. Barker et al. (2000) and Drobnic et al. (2005) were double-blind trials, however, Orriols et al. (2015) states that it was single-masked with no further information on who was blinded.

The number of participants in each study was generally small (n=30 to 74). The duration of treatment and follow-up varied between the studies. Barker et al. (2000) was short (4 weeks' treatment with 2 week follow-up) compared with 6 months' treatment with 6-month follow-up with Drobnic et al. (2005) and 3 months' treatment with 12-month follow-up with Orriols et al. (2015). The varying treatment duration across the studies makes it difficult to determine the optimum duration of treatment.

Barker et al. (2000) followed a 28-day treatment cycle as recommended in the SPC for TOBI (nebuliser solution) when used for treating pulmonary infections caused by *P aeruginosa* in people cystic fibrosis bronchiectasis. Drobnic et al. (2005) and Orriols et al. (2015) used longer treatment durations and did not include a 28-day treatment free period after the first 28 days of treatment. Specialists who commented on this evidence summary suggested that there is some variation in practice for including a treatment free period after the initial treatment period with tobramycin. Some specialist centres include a treatment free period after initial period of treatment, and others take a pragmatic approach and assess the person's clinical response after a month.

The dose and frequency of inhaled tobramycin, 300 mg twice daily, was the same for all the included studies. Two of the included studies used the TOBI brand of tobramycin nebuliser solution, whereas 1 study used an intravenous preparation of tobramycin (Tobragobens; not available in the UK) that was diluted to make a solution that could be administered via a nebuliser. The dose of tobramycin used in the studies is the same as that used for the licensed indications for the nebulised preparations Bramitob and TOBI. The licensed dose of Vantobra while different, is
bioequivalent to the licensed dose of TOBI nebuliser solution (personal communication PARI Pharma GmbH, March 2017). There is no published evidence looking at the use of TOBI podhaler for treating infective exacerbations caused by *P aeruginosa* in people with non-cystic fibrosis bronchiectasis.

Inclusion criteria were similar between the 3 studies in that they all included adults with non-cystic fibrosis bronchiectasis producing purulent sputum containing *P aeruginosa*. The crossover study by Drobnic et al. (2005) included participants that had exacerbations and infections that were difficult to control in the long-term. This group of participants would have similar criteria to that recommended by the British Thoracic Society to be considered for long-term nebulised therapy. The presence of mucopurulent or purulent sputum alone or the isolation of a pathogen alone is not necessarily an indication for antibiotic treatment (British Thoracic Society). The exclusion criteria and baseline characteristics differed between the 3 studies which may complicate the direct comparison of the results. In addition, the geographical population studied were either American or Spanish which limits the applicability of the findings to the UK population.

Drobnic et al. (2005) and Orriols et al. (2015) treated participants with intravenous ceftazidime and tobramycin for 2 weeks to achieve a stable condition before receiving the study medicine. However, use of antibiotics within 2 weeks of screening was an exclusion criteria in the study by Barker et al. (2000). Specialists who commented on this evidence summary highlighted that the administration of intravenous antibiotics before starting inhaled tobramycin as carried out by Drobnic et al. (2005) and Orriols et al. (2015) does not reflect routine practice and may have affected the outcomes in these studies. The same antibiotics (intravenous ceftazidime and tobramycin) were used to treat exacerbations that resulted in an admission to hospital during the study by Drobnic et al. (2005). Treatment of exacerbations while on nebulised treatment is a common intervention in clinical practice, reflected in the studies by Drobnic et al. (2005) and Orriols et al. (2015).

Drobnic et al. (2005) and Orriols et al. (2015) reported clinical outcomes such as exacerbations and hospitalisation. However, Barker et al. (2000) reported sputum *P aeruginosa* density only. The tools used to measure patient health-related outcomes varied across the studies. Drobnic et al. (2005) and Orriols et al. (2015) used the St George's respiratory questionnaire (SGRQ) to assess the participant's general health condition whereas Barker et al. (2000) did not use a validated tool.

Three clinical trials are underway investigating inhaled tobramycin for treating non-cystic fibrosis bronchiectasis (NCT01677403, NCT02657473 and NCT02712983).

An overview of the quality assessment of each included study can be found in evidence tables.
Estimated impact for the NHS

Other medicines

The British Thoracic Society (BTS) guideline for non-cystic fibrosis bronchiectasis recommends that people with non-cystic fibrosis bronchiectasis who have 3 or more exacerbations per year that need antibiotic therapy, or who have fewer exacerbations that are causing significant morbidity, should be considered for long-term oral or nebulised antibiotics. The choice of antibiotic should be guided by the results of tests for antibiotic sensitivity. Oral antibiotics used for first-line treatment are amoxicillin, co-amoxiclav or flucloxacillin. Nebulised antibiotics are tobramycin, gentamicin and colistimethate sodium (BTS guideline for non-cystic fibrosis bronchiectasis). See individual summary of product characteristics for licensed indications.

Specialists involved in the production of this evidence summary commented that oral antibiotics would be the preferred option for non-

Pseudomonas

infections or when

P aeruginosa

has been cultured for the first time. Specialists also commented that there are fewer oral antibiotic options for treating

P aeruginosa

infections. In practice there are more intravenous and nebulised preparations of anti-pseudomonal antibiotics and these are often the preferred routes of administration to treat difficult

P aeruginosa

infections. There is no published evidence for using TOBI podhaler to treat non-cystic fibrosis bronchiectasis.

Costs of other medicines

No cost effectiveness studies of inhaled tobramycin for treating non-cystic fibrosis bronchiectasis were identified.

Table 3 shows the cost of inhaled antibiotics used for long-term treatment of non-cystic fibrosis bronchiectasis in adults. The optimal duration of treatment could not be determined from the studies included in this evidence summary because treatment durations varied from 4 weeks to 6 months. A 28-day treatment duration has been used to compare costs of treatment options, none of which are specifically licensed for treating infective exacerbations caused by

P aeruginosa

in people with non-cystic fibrosis bronchiectasis.

Specialists who commented on this evidence summary suggested that intravenous preparations of tobramycin have been used off-label as nebulised therapy in the past; some centres still use the phenol-free intravenous preparation as nebulised treatment because it is more cost-effective when compared to tobramycin nebuliser solution. Specialists also commented that although using the intravenous preparation of tobramycin is cost-effective, prescribers need to consider the risks
associated with prescribing an intravenous preparation off-label and administering this by a different route than it was intended for, against prescribing a licensed nebuliser solution for off-label use.

Table 3 Costs of other medicines

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Usual dose</th>
<th>28-day cost excluding VAT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nebulised</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin (TOBI [nebuliser solution])</td>
<td>300 mg twice daily</td>
<td>£1,305.92</td>
</tr>
<tr>
<td>Tobramycin (Bramitob)</td>
<td>300 mg twice daily</td>
<td>£1,187.00</td>
</tr>
<tr>
<td>Tobramycin (Vantobra)</td>
<td>170 mg twice daily</td>
<td>£1,305.00</td>
</tr>
<tr>
<td>Tobramycin solution for injection (generic)</td>
<td>80 mg to 160 mg twice daily</td>
<td>£211.12 to £422.24</td>
</tr>
<tr>
<td>Gentamicin solution for injection (generic)</td>
<td>80 mg twice daily</td>
<td>£56.00</td>
</tr>
<tr>
<td>Colistimethate sodium (Promixin)</td>
<td>1 to 2 million International Units twice daily</td>
<td>£313.60 to £627.20</td>
</tr>
<tr>
<td><strong>Dry powder for inhalation</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin (TOBI podhaler)</td>
<td>112 mg twice daily</td>
<td>£1790.00</td>
</tr>
</tbody>
</table>
The doses shown do not represent the full range that can be used and they do not imply therapeutic equivalence.

The costs shown in the table are for the medicines only (excluding VAT) and do not include any local procurement discounts or other costs incurred, such as dilution and administration, standard supportive therapy, or attendance for day case treatment.

Dosage for the TOBI brand of tobramycin nebuliser solution is that used in the studies.

Costs taken from the Drug Tariff March 2017; excluding VAT, NHS indicative prices.

Dosages for the Bramitob and Vantobra brands of tobramycin nebuliser solution are based on the dose used for their licensed indications in the relevant SPCs.

Costs taken from MIMS March 2017; excluding VAT, NHS indicative prices.

Intravenous preparation is not licensed for use as a nebuliser. See the SPCs for tobramycin and gentamicin for further information.

Dose based on information provided by specialists.

Costs are based on the 80 mg (2 ml) vial and are taken from the BNF March 2017; excluding VAT, NHS indicative prices.

Dosages taken from the British Thoracic Society (BTS) guideline for non-cystic fibrosis bronchiectasis.

Costs are taken from the BNF March 2017; excluding VAT, NHS indicative prices.

**Current or estimated usage**

Estimating current usage of inhaled tobramycin for treating infective exacerbations caused by *P. aeruginosa* in non-cystic fibrosis bronchiectasis is difficult because inhaled tobramycin is used to treat infective exacerbations in cystic fibrosis. No information on prescribing inhaled tobramycin for treating non-cystic fibrosis bronchiectasis was available at the time this evidence summary was prepared.

Specialists involved in the production of this evidence summary suggested that inhaled tobramycin for treating infective exacerbations caused by *P. aeruginosa* in people non-cystic fibrosis bronchiectasis is used in small numbers in specialist centres that treat bronchiectasis.

**Likely place in therapy**

The BTS guideline for non-cystic fibrosis bronchiectasis does not specify the preferred nebulised antibiotic of choice for long-term treatment of non-cystic fibrosis bronchiectasis; the choice of antibiotic should be guided by the results of tests for antibiotic sensitivity. There are no licensed
inhaled preparations of antibiotics for non-cystic fibrosis bronchiectasis. Tobramycin and colistimethate sodium are available as nebuliser solutions and dry powder respectively for inhalation, licensed only for pulmonary infections caused by *P. aeruginosa* in people with cystic fibrosis. Gentamicin is suggested as an alternative antibiotic for long-term use. The cost of gentamicin is lower compared with tobramycin and colistimethate sodium, but its intravenous preparation is not licensed to be used as a nebuliser solution.

The summaries of product characteristics for tobramycin advise that consideration should be given to official guidance regarding the appropriate use of antibacterial agents. NICE has produced guidelines on antimicrobial stewardship: systems and processes for effective antimicrobial medicine use and on antimicrobial stewardship: changing risk-related behaviours in the general population.

The studies included in this evidence summary suggest that inhaled tobramycin may be effective for treating *P. aeruginosa* infections in some people with non-cystic fibrosis bronchiectasis; the evidence is of variable quality, has many limitations, and it is difficult to draw any firm conclusions from it.

The adverse effects seen in the studies reflect those listed in the summaries of product characteristics for tobramycin. Four deaths in people using tobramycin and 1 death in a person using placebo caused by respiratory failure were reported during the studies, however it was not clear if the deaths were considered related to the study medication. Eleven withdrawals due to adverse effects were reported with tobramycin in the studies (mainly because of bronchospasm) compared with 2 withdrawals with placebo.

Specialists who commented on this evidence summary suggested that in practice, when nebulised treatment is indicated for *P. aeruginosa* infections in people with non-cystic fibrosis bronchiectasis, inhaled tobramycin is considered when treatment with other nebulised therapy is not tolerated, if the condition is deteriorating while on other nebulised antibiotics, or if cultures are sensitive to tobramycin. Off-label use of intravenous preparations of gentamicin and dry powder for inhalation preparation of colistimethate sodium administered as nebulised treatment are used in practice ahead of inhaled tobramycin because of their lower cost.

While the acquisition cost of nebulised tobramycin is more than that of other inhaled antibiotics that are recommended by the BTS for non-cystic-fibrosis bronchiectasis, many factors need taking into account. Local decision makers need to take safety, efficacy, cost and patient factors into account when considering the likely place in therapy of inhaled tobramycin for non-cystic fibrosis bronchiectasis.
Information for the public about medicines

Evidence summaries provide an overview of the best evidence that is available about specific medicines. They also give general information about the condition that the medicine might be prescribed for, how the medicine is used, how it works, and what the aim of treatment is.

Evidence summaries aim to help healthcare professionals and patients decide whether medicines are safe to use and if they are likely to work well, especially when there isn’t another suitable medicine that has a licence for the condition. They don't contain recommendations from NICE on whether the medicine should be used.

Information about licensing of medicines

In the UK, medicines need to have a licence before they can be widely used. To get a licence, the manufacturer of the medicine has to provide evidence that shows that the medicine works well enough and is safe enough to be used for a specific condition and for a specific group of patients, and that they can manufacture the medicine to the required quality. Evidence summaries explain whether a medicine has a licence, and if it does what the licence covers.

There is more information about licensing of medicines on NHS Choices.

Medicines can be prescribed if they don't have a licence (unlicensed) or for 'off-label' use. Off-label means that the person prescribing the medicine wants to use it in a different way than that stated in its licence. This could mean using the medicine for a different condition or a different group of patients, or it could mean a change in the dose or that the medicine is taken in a different way. If a healthcare professional wants to prescribe an unlicensed medicine, or a licensed medicine off-label, they must follow their professional guide, for example for doctors the General Medical Council’s good practice guidelines. These include giving information about the treatment and discussing the possible benefits and harms so that the person has enough information to decide whether or not to have the treatment. This is called giving informed consent.

Questions that might be useful to ask about medicines

- Why am I being offered this medicine?
- Why am I being offered a medicine that is unlicensed or is being used off-label?
- What does the treatment involve?
• What are the benefits I might get?

• How good are my chances of getting those benefits?

• Could having the treatment make me feel worse?

• Are there other treatments I could try?

• What are the risks of the treatment?

• Are the risks minor or serious? How likely are they to happen?

• What could happen if I don’t have the treatment?

Relevance to other NICE programmes

The use of inhaled tobramycin for non-cystic fibrosis bronchiectasis is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

NICE has issued guidance on:

• Antimicrobial stewardship: changing risk-related behaviours in the general population (2017) NICE guideline NG63.

• Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use (2015) NICE guideline NG15.

• Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (2013) NICE technology appraisal guidance 276.

NICE has not issued any guidelines on non-cystic fibrosis bronchiectasis but has published the following advice relating to this condition:


References


Evidence tables

**Table 4 Barker et al. 2000**

<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Unique identifier</td>
<td>n/a</td>
</tr>
<tr>
<td>Study type</td>
<td>RCT</td>
</tr>
<tr>
<td>Aim of the study</td>
<td>To evaluate the microbiological efficacy and safety of inhaled tobramycin for treatment of patients with non-CF bronchiectasis and <em>P aeruginosa</em></td>
</tr>
</tbody>
</table>
### Study dates
8-week study period, 2 weeks for screening, 4 weeks' treatment phase, 2 weeks' follow-up

### Setting
Across 16 sites in the US
Tobramycin was self-administered at home by the participants

### Number of participants
74

### Population
Adults (91.9% white participants) with non-CF bronchiectasis with purulent sputum.
125 participants were screened and 74 participants (60.8% female) with a mean age 66.6 years (tobramycin group) and 63.2 years (placebo group) were enrolled

### Inclusion criteria
Adults with bronchiectasis diagnosed by conventional or high-resolution computed tomography and sputum containing at least \(10^4\) cfu \(P. aeruginosa\) per gram

### Exclusion criteria
Adults with CF, allergic bronchopulmonary aspergillosis, acute pulmonary process requiring medical intervention as indicated by a new infiltrate on a chest radiograph, significant recent haemoptysis, or had received antibiotics within 2 weeks of the screening visit

### Intervention(s)
Tobramycin 300 mg via a jet nebuliser, twice daily for 4 weeks (n=37)

### Comparator(s)
Placebo via a jet nebuliser, twice a day for 4 weeks (n=37)

### Length of follow-up
Participants were observed for 2 weeks after administration of their last dose

### Outcomes
**Primary outcome:**
- Change in \(P. aeruginosa\) density from baseline to week 4 (expressed as \(\log_{10}\) cfu/g sputum)
Secondary outcomes:
- Change in *P. aeruginosa* density from baseline values to week 2 and to week 6
- Investigator's subjective assessment of a change in the patient's general medical condition ("improved" or "not improved") at week 6
- Percent change in FEV₁ percent predicted and in FVC percent predicted from week 0 to week 4 calculated by dividing actual values by the values predicted by the Knudson equation for healthy individuals
- Microbiological response

Safety outcomes:
- Incidence of adverse events, change in serum chemistry and haematology measurements, and airway reactivity

<table>
<thead>
<tr>
<th>Source of funding</th>
<th>PathoGenesis Corporation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall risk of bias/quality assessment (CASP RCT checklist)</td>
<td></td>
</tr>
<tr>
<td>Did the trial address a clearly focused issue?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the assignment of participants to treatments randomised?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were participants, health workers and study personnel blinded?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were the groups similar at the start of the trial?</td>
<td>Yes</td>
</tr>
<tr>
<td>Aside from the experimental intervention, were the groups treated equally?</td>
<td>Yes</td>
</tr>
<tr>
<td>Were all of the participants who entered the trial properly accounted for at its conclusion?</td>
<td>Yes</td>
</tr>
<tr>
<td>How large was the treatment effect?</td>
<td>See table 7</td>
</tr>
<tr>
<td>How precise was the estimate of the treatment effect?</td>
<td>See table 7</td>
</tr>
<tr>
<td>Can the results be applied in your context? (or to the local population)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were all clinically important outcomes considered?</td>
<td>No</td>
</tr>
</tbody>
</table>
## Study limitations

- Small study with short period of 2 weeks follow-up
- The investigator assessment was subjective
- Limited to adults only
- Exclusion of people with the conditions mentioned under 'exclusion criteria' may limit the applicability of the study findings to populations that have such conditions
- Included participants received at least 1 dose of either tobramycin or placebo
- No validated tool used to assess improvements in participants' condition

<table>
<thead>
<tr>
<th>Are the benefits worth the harms and costs?</th>
<th>See key points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study limitations</td>
<td></td>
</tr>
</tbody>
</table>

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**Comments**

- **a** Tobramycin (TOBI) formulation used was non-pyrogenic, preservative-free, pH-adjusted solution designed for inhalation.
- **b** Assessed by categorising *P. aeruginosa* to 'eradicated, reduced by treatment or did not respond to treatment'. *P. aeruginosa* was considered eradicated if it was not detected at week 6; if sputum was not produced at week 6 and; *P. aeruginosa* was not isolated at week 4. Participants response was defined as reduced by treatment if *P. aeruginosa* was recovered from the week 6 sputum sample but was reduced by at least 2 log<sub>10</sub> cfu/g at week 4 compared with baseline. No medical response was defined as *P. aeruginosa* not decreasing by 2 log<sub>10</sub> cfu/g at week 4 or if the participant withdrew from the study.
- **c** The number of exacerbations or admissions not reported as an outcome but discussed in the study.

  - At each visit a sputum sample was obtained and the density of the *P. aeruginosa* in sputum was measured. Tobramycin levels were measured
  - Adherence was measured at week 4 by counting the number of vials of study medicine used. More than 80% of tobramycin doses were used by 81% (n=30) and 86% (n=32) of the tobramycin and the placebo groups respectively
  - There were 6 participants who withdrew from the tobramycin group (3 for adverse events, 2 for use of antibiotics other than study medicine, and 1 was lost to follow-up) and 8 withdrew from the placebo group (2 for adverse events, and 6 for use of antibiotics other than the study medicine)
  - Measurements of *P. aeruginosa* sputum density from week 0 were used as the baseline value unless unavailable, in which case the measurement at the screening visit was used
  - Bacterial resistance was not listed as an outcome, however, the authors assessed it using the minimum inhibitory concentration value for parenteral tobramycin, 16 micrograms/ml or more. A value has not been established for inhaled tobramycin.

**Abbreviations:** cfu/g, colony-forming unit per gram; CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; RCT, randomised controlled trial.

**Table 5** Drobnic et al. 2005
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Unique identifier</td>
<td>n/a</td>
</tr>
<tr>
<td>Study type</td>
<td>RCT-controlled crossover study with 1-month washout period</td>
</tr>
<tr>
<td>Aim of the study</td>
<td>To determine the clinical effectiveness and safety of 6-month aerosol tobramycin therapy in the treatment of chronic bronchial infection with <em>P. aeruginosa</em> in non-cystic fibrosis participants with bronchiectasis</td>
</tr>
<tr>
<td>Study dates</td>
<td>Study treatment duration was 13 months (2 cycles of 6 months with 1 month washout period) and participants were followed up for 6 months after the study</td>
</tr>
<tr>
<td>Setting</td>
<td>Spain</td>
</tr>
<tr>
<td>Number of participants</td>
<td>30</td>
</tr>
<tr>
<td>Population</td>
<td>Adults with non-CF bronchiectasis producing purulent sputum Mean age of participants completing treatment was 64.5 years</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Adults with bronchiectasis diagnosed by high-resolution computed tomography who had 3 or more positive sputum cultures for <em>P. aeruginosa</em> during 6 months before the study</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Participants with CF, tobramycin hypersensitivity, <em>P. aeruginosa</em> in sputum resistant to tobramycin, auditory threshold in either ear greater than 20 dB at frequencies between 500 and 8000 Hz or had a serum creatinine of 1.5 mg/dL or more</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Tobramycin 300 mg via a jet nebuliser, twice a day for 6 months^a^</td>
</tr>
<tr>
<td>Comparator(s)</td>
<td>Placebo via a jet nebuliser, twice a day for 6 months</td>
</tr>
<tr>
<td>Length of follow-up</td>
<td>6 months after completing the study</td>
</tr>
</tbody>
</table>
### Outcomes

<table>
<thead>
<tr>
<th>Primary outcome:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Number of exacerbations (defined as 'more frequent coughing, more dyspnoea and an increase in sputum volume and purulence')</td>
</tr>
<tr>
<td>- Number and days of hospital admissions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Pulmonary function tests (FEV₁ and FVC) measured in accordance with American Thoracic Society standards</td>
</tr>
<tr>
<td>- Days of antibiotic treatment</td>
</tr>
<tr>
<td>- Quality of life assessed using SGRQ</td>
</tr>
<tr>
<td>- Density of <em>P. aeruginosa</em> in sputum</td>
</tr>
<tr>
<td>- Emergence of bacterial resistance and other opportunistic bacteria</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Safety outcomes:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Incidence of bronchospasm</td>
</tr>
<tr>
<td>- Other adverse events such as ototoxicity and nephrotoxicity</td>
</tr>
</tbody>
</table>

### Source of funding

Not stated

### Overall risk of bias/quality assessment (CASP RCT checklist)

<table>
<thead>
<tr>
<th>Question</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Did the trial address a clearly focused issue?</td>
<td>Yes</td>
</tr>
<tr>
<td>Was the assignment of participants to treatments randomised?</td>
<td>Unclear&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Were participants, health workers and study personnel blinded?</td>
<td>Unclear&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Were the groups similar at the start of the trial?</td>
<td>Unclear&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aside from the experimental intervention, were the groups treated equally?</td>
<td>Unclear&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Were all of the patients who entered the trial properly accounted for at its conclusion?</td>
<td>Yes</td>
</tr>
<tr>
<td>How large was the treatment effect?</td>
<td>See table 8</td>
</tr>
<tr>
<td>How precise was the estimate of the treatment effect?</td>
<td>See table 8</td>
</tr>
<tr>
<td>Can the results be applied in your context? (or to the local population)</td>
<td>Unclear</td>
</tr>
<tr>
<td>Were all clinically important outcomes considered?</td>
<td>Yes</td>
</tr>
<tr>
<td>Are the benefits worth the harms and costs?</td>
<td>See key points</td>
</tr>
</tbody>
</table>

**Study limitations**
- Small study with a high number of dropouts (n=10)
- Only applicable to adults with non-CF bronchiectasis who have had intravenous treatment with antibiotics before use of inhaled tobramycin
- Assessment of some outcome measures such as emergence of resistance not adequately reported

**Comments**
- Tobramycin (Tobragobens, 100 mg/2 ml) was diluted in 0.9% sodium chloride to obtain an 8 ml solution. The authors report that this formulation was intravenous preparation containing metasulfites.
- Details of randomisation and blinding not reported in the study.
- All participants in the study were hospitalised and completed 2 weeks of intravenous treatment with ceftazidime and tobramycin prior entry into the study to achieve stable status.
- No power estimation performed in the study as the authors report that the outcome of therapeutic interventions in bronchiectasis patients has not been well established, therefore the aim of the study was mainly exploratory.
- Three participants withdrew from the study during the tobramycin period due to adverse events.
- The authors report that main efficacy outcomes were also compared in a parallel design study.
### Table 6 Orriols et al. 2015

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Unique identifier</td>
<td>EU clinical trial register number 2005-005820-15</td>
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<tr>
<td>Study type</td>
<td>RCT</td>
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<tr>
<td>Aim of the study</td>
<td>To evaluate the efficacy of a 3-month treatment with nebulised tobramycin following a short course of intravenous antibiotics for the eradication of <em>P aeruginosa</em> in non-CF bronchiectasis</td>
</tr>
<tr>
<td>Study dates</td>
<td>March 2006 to March 2009, total 15 months duration</td>
</tr>
<tr>
<td>Setting</td>
<td>Spain, tertiary university hospital</td>
</tr>
<tr>
<td>Number of participants</td>
<td>35</td>
</tr>
<tr>
<td>Population</td>
<td>Adults with non-CF bronchiectasis with purulent sputum. Of the 35 participants, 54.3% were male and 45.7% were female. The mean age was 69.36 years (tobramycin group) and 70.11 years (placebo group)</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Adults over 18 years old with high-resolution computed tomography confirmed non-CF bronchiectasis with first isolation of <em>P aeruginosa</em> in sputum (non-mucoid)</td>
</tr>
<tr>
<td>Exclusion criteria</td>
<td>Infection with other Gram-negative non-fermenter bacteria, mucoid <em>P aeruginosa</em> or microorganisms resistant to any of the antibiotics used in the study, concomitant use of quinolones, chronic treatment with macrolides, and abnormal kidney and auditory function test results</td>
</tr>
<tr>
<td>Intervention(s)</td>
<td>Tobramycin 300 mg via a jet nebuliser, twice a day for 3 months&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Comparator(s)</td>
<td>Placebo via a jet nebuliser, twice a day for 3 months</td>
</tr>
</tbody>
</table>

---

**Abbreviations:** cfu/g, colony-forming unit per gram; CF, cystic fibrosis; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; RCT, randomised controlled trial; SGRQ, St George’s respiratory questionnaire.
Length of follow-up | 12 months after completing treatment (total length of study 15 months)
---|---
Outcomes | There was no differentiation between primary and secondary outcomes in the study
| • Eradication rate of *P aeruginosa*
| • Number of exacerbations (defined as 'more frequent coughing, more dyspnoea and an increase in sputum volume and purulence')
| • Number of hospital admissions and days of hospitalisation
| • Pulmonary function tests, FEV₁ and FVC measured in accordance with American Thoracic Society standards
| • Quality of life assessed using SGRQ
| • Days of antibiotic use

Safety outcomes
| • Bronchospasm
| • Auditory changes

Source of funding | Not stated

Overall risk of bias/quality assessment (CASP RCT checklist)
| Did the trial address a clearly focused issue? | Yes
| Was the assignment of participants to treatments randomised? | Yes
| Were participants, health workers and study personnel blinded? | Unclear \(^b\)
| Were the groups similar at the start of the trial? | Yes
| Aside from the experimental intervention, were the groups treated equally? | Unclear \(^c\)
| Were all of the participants who entered the trial properly accounted for at its conclusion? | Yes
| How large was the treatment effect? | See table 9
### Study limitations

- Small study
- Additional systemic therapy used during intervention
- Only applicable to adults with non-CF bronchiectasis who have had intravenous treatment with antibiotics before use of inhaled tobramycin
- The assessment of some outcomes such as eradication rate not adequately reported in the study

### Comments

- Nebulised formulation of tobramycin (TOBI) used in the study.
- The study was described as a single-masked study. Treatment assignment was blinded until completion of the study, but it was unclear to who the treatment was blinded to.
- Participants in each group were allowed additional antibiotics if needed.
  - All participants were treated with intravenous ceftazidime and tobramycin for 14 days during the first 4 weeks of initial detection of *P. aeruginosa*
  - A short acting bronchodilator was administered approximately 1 hour before nebulised tobramycin
  - Supplementary use of oral antibiotics was allowed on the development of an exacerbation defined as more frequent coughing, greater dyspnoea and an increase in sputum volume and purulence
  - 5 participants withdrew due to bronchospasm during the first month of tobramycin treatment (these participants had worse FEV₁ than the rest of the participants) and 2 participants from the placebo group abandoned the study in the first month.
**Abbreviations:** CF, cystic fibrosis; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; RCT, randomised controlled trial; SGRQ, St George’s respiratory questionnaire.

## Results tables

### Table 7 Barker et al. 2000

<table>
<thead>
<tr>
<th></th>
<th>Inhaled tobramycin 300 mg twice daily</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>37</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

### Primary outcome

Mean change in *P. aeruginosa* sputum density from baseline to week 4

<table>
<thead>
<tr>
<th></th>
<th>Inhaled tobramycin 300 mg twice daily</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>37</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

### Selected secondary outcomes

Investigator’s subjective assessment of a change in the patient’s general medical condition ("improved" or "not improved" at week 6)

<table>
<thead>
<tr>
<th></th>
<th>Inhaled tobramycin 300 mg twice daily</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>37</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>

### Safety and tolerability outcomes

<table>
<thead>
<tr>
<th></th>
<th>Inhaled tobramycin 300 mg twice daily</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>37</td>
<td>37</td>
<td></td>
</tr>
</tbody>
</table>
### Table 8 Drobnic et al. 2005

<table>
<thead>
<tr>
<th></th>
<th>Tobramycin 300 mg twice daily</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>20 completed treatment&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number of exacerbations&lt;sup&gt;b&lt;/sup&gt; per participant</td>
<td>0.9</td>
<td>1.3</td>
<td>p=0.330, NS</td>
</tr>
<tr>
<td>Mean number (±SD) of hospital admissions per participant</td>
<td>0.15 ± 0.37</td>
<td>0.75 ± 1.16</td>
<td>p=0.038</td>
</tr>
</tbody>
</table>

<sup>a</sup> Includes 6 and 8 participants in the tobramycin and placebo groups, respectively, who withdrew from the study.

<sup>b</sup> n=35, 2 participants were not evaluated in the placebo group; 1 who had *P. aeruginosa* at screening was found to have a negative culture 2 weeks later at baseline, and 1 who did not have a sample collected at week 4.

**Abbreviations:** CI, confidence interval; cfu/g, colony-forming unit per gram; FEV<sub>1</sub>, forced expiratory volume in 1 second; FVC, forced vital capacity; NS, not statistically significant; OR, odds ratio.
<table>
<thead>
<tr>
<th>Mean (±SD) number of days of admission per participant</th>
<th>2.05 ± 5.03</th>
<th>12.65 ± 21.8</th>
<th>p=0.047</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Selected secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (±SD) number of days of antibiotic use</td>
<td>8.4 ± 11.2</td>
<td>19.1 ± 24.4</td>
<td>p=0.052, NS</td>
</tr>
<tr>
<td>Percent change in FEV$_1$, median (range)</td>
<td>−3.50 (−5.95 to −1.02)</td>
<td>−1.20 (−4.38 to −1.98)</td>
<td>p=0.240, NS</td>
</tr>
<tr>
<td>Percent change in FVC, median (range)</td>
<td>−5.45 (−8.03 to −2.87)</td>
<td>−1.30 (−4.88 to −2.28)</td>
<td>p=0.056, NS</td>
</tr>
<tr>
<td>Mean (±SD) change in St George's respiratory questionnaire total score</td>
<td>−0.90 ± 3.93</td>
<td>−0.83 ± 6.89</td>
<td>p=0.97, NS</td>
</tr>
<tr>
<td><strong>Safety and tolerability outcomes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>20 completed the study</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Number of participants with bronchospasm</td>
<td>3</td>
<td>0</td>
<td>Not reported</td>
</tr>
</tbody>
</table>

$^a$ 30 participants were originally enrolled in the study but there were 10 drop outs. This analysis is based on the 20 participants who completed both treatment periods.

$^b$ Exacerbation was defined as 'more frequent coughing, more dyspnoea and an increase in sputum volume and purulence'.

**Abbreviations:** FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; NS, not statistically significant; SD, standard deviation.

Table 9 Orriols et al. 2015

<table>
<thead>
<tr>
<th></th>
<th>Tobramycin 300 mg twice daily</th>
<th>Placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>16</td>
<td>19</td>
<td></td>
</tr>
</tbody>
</table>

**Outcomes**

Percentage of participants with $P$ aeruginosa eradicated at the end of the study 54.5% 29.4% Not reported
### Number of exacerbations (mean ± SD)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Number of Exacerbations (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>1.27 ± 1.62</td>
</tr>
<tr>
<td>Group B</td>
<td>2.5 ± 1.63</td>
</tr>
</tbody>
</table>

*p=0.04*

### Number of admissions (mean ± SD)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Number of Admissions (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>0.06 ± 0.25</td>
</tr>
<tr>
<td>Group B</td>
<td>0.47 ± 0.51</td>
</tr>
</tbody>
</table>

*p=0.04*

### Days of hospitalisation (mean ± SD)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Days of Hospitalisation (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>0.90 ± 3.01</td>
</tr>
<tr>
<td>Group B</td>
<td>13.56 ± 22.64</td>
</tr>
</tbody>
</table>

*p=0.03*

### Days of antibiotic use (mean ± SD)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Days of Antibiotic Use (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>8.4 ± 11.2</td>
</tr>
<tr>
<td>Group B</td>
<td>19.1 ± 24.4</td>
</tr>
</tbody>
</table>

*p=0.052, NS*

### Percent change in FEV₁, (mean ± SD)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Percent Change in FEV₁, (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>−0.78 ± 5.12</td>
</tr>
<tr>
<td>Group B</td>
<td>1.46 ± 6.23</td>
</tr>
</tbody>
</table>

*p=0.36, NS*

### Percent change in FVC, (mean ± SD)

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Percent Change in FVC, (mean ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>−2.55 ± 6.26</td>
</tr>
<tr>
<td>Group B</td>
<td>1.35 ± 12.17</td>
</tr>
</tbody>
</table>

*p=0.36, NS*

### Mean (±SD) change in SGRQ total score

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Mean (±SD) Change in SGRQ Total Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>−14.6 ± 27.9</td>
</tr>
<tr>
<td>Group B</td>
<td>−4.9 ± 26.4</td>
</tr>
</tbody>
</table>

*p=0.31, NS*

### Safety and tolerability outcomes

Not reported adequately in the study. See evidence review section

\(^{a}\) Exacerbation was defined as 'more frequent coughing, more dyspnoea and an increase in sputum volume and purulence'.

**Abbreviations**: FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; NS, not statistically significant; SD, standard deviation; SGRQ, St George’s respiratory questionnaire.

### Excluded studies

<table>
<thead>
<tr>
<th>Study Reference</th>
<th>Reason for Exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Berlana D, Llop JM, Manresa F, et al. (2011)</td>
<td>Population did not meet the inclusion criteria</td>
</tr>
</tbody>
</table>

Excluded studies: Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12) © NICE 2018. All rights reserved. Subject to Notice of rights (https://www.nice.org.uk/terms-and-conditions#notice-of-rights). Page 36 of 68
<table>
<thead>
<tr>
<th>Reference</th>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiel SB</td>
<td>The relationship between antimicrobial efficacy and improved medical condition in tobramycin solution for inhalation therapy in bronchiectasis Eur Resp J; 2000; 16 (Sup 31): S4 S 94.</td>
</tr>
<tr>
<td>Study</td>
<td>Notes</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Wurzel D, Marchant JM, Yerkovich ST, et al. (2011) Short courses of antibiotics for children and adults with bronchiectasis Cochrane systematic reviews 15(6).</td>
<td>Systematic review did not meet inclusion criteria</td>
</tr>
</tbody>
</table>

**Terms used in this evidence summary**

**Exacerbation**

Drobnic et al. (2005) and Orriols et al. (2015) defined exacerbation as more frequent coughing, more dyspnoea (shortness of breath) and an increase in sputum volume and purulence.

**St George's respiratory questionnaire (SGRQ)**

This is a quality of life questionnaire which consists of 76 items rated on a scale 0 to 100, divided into 3 domains: respiratory symptoms, activities, and social and psychological impact. A higher score indicates a poorer quality of life (Wilson et al. 1997).
Search strategy

Database: Medline

Platform: Ovid

Version: 1946 to November Week 5 2016

Search date: 12/12/2016

Number of results retrieved: 58

Search strategy:

1 "47663".tw. (6)

2 "I 47663".tw. (0)

3 ("nebramycin factor 6" or "nebramycin factor VI").tw. (8)

4 aktob*.tw. (16)

5 ak-tob*.tw. (0)

6 alveoterol*.tw. (0)

7 artobin*.tw. (0)

8 bactob*.tw. (53)

9 bethkis*.tw. (3)

10 bralifex*.tw. (0)

11 bramicil*.tw. (0)

12 bramitob*.tw. (7)
| 13 | briedu*.tw. (0) |
| 14 | brulamycin*.tw. (13) |
| 15 | colther*.tw. (0) |
| 16 | dartobcin*.tw. (0) |
| 17 | eltol*.tw. (1) |
| 18 | eyebrex*.tw. (0) |
| 19 | fotex*.tw. (0) |
| 20 | fytopra*.tw. (0) |
| 21 | gernebcin*.tw. (1) |
| 22 | gotabiotic*.tw. (0) |
| 23 | ibrex*.tw. (0) |
| 24 | ikobel*.tw. (0) |
| 25 | kitabis*.tw. (0) |
| 26 | mytob*.tw. (0) |
| 27 | mytocin*.tw. (0) |
| 28 | nebacin*.tw. (0) |
| 29 | nebucin*.tw. (11) |
| 30 | nebic*.tw. (19) |
| 31 | nebris*.tw. (2) |
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

70 consac.tw. (5)

71 defy.tw. (954)

72 cromycin.tw. (0)

73 distobram.tw. (1)

74 dilaterol.tw. (0)

75 eotob.tw. (0)

76 eyetobrin.tw. (0)

77 glytob.tw. (0)

78 intob.tw. (1)

79 isenia.tw. (1)

80 klonamicin.tw. (0)

81 mdas.tw. (470)

82 micitrex.tw. (0)

83 monobracin.tw. (0)

84 monotobrin.tw. (0)

85 obra.tw. (497)

86 obry.tw. (11)

87 ocusyn.tw. (0)

88 ocutob.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)
108 bronchiect*tw. (7624)

109 bronchoect*tw. (29)

110 (kartagener* adj4 syndrome*).tw. (740)

111 (cilia* adj4 dyskines*).tw. (1111)

112 (bronch* adj4 dilat*).tw. (1016)

113 (young* adj syndrome*).tw. (91)

114 exp Bronchiectasis/ (8692)

115 Ciliary Motility Disorders/ (1018)

116 or/1-107 (31283)

117 or/108-115 (13419)

118 116 and 117 (84)

119 Animals/ not (Animals/ and Humans/) (4636432)

120 118 not 119 (84)

121 120 (84)

122 limit 121 to english language (58)

Database: Medline in-process

Platform: Ovid

Version: Epub Ahead of Print <December 09, 2016>

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <December 09, 2016>, Ovid MEDLINE(R) Daily Update <December 07, 2016>
Search date: 12/12/2016

Number of results retrieved: 5

Search strategy:

1 "47663".tw. (0)

2 "I 47663".tw. (0)

3 ("nebramycin factor 6" or "nebramycin factor VI").tw. (0)

4 aktob*.tw. (6)

5 ak-tob*.tw. (0)

6 alveoterol*.tw. (0)

7 artbin*.tw. (0)

8 bactob*.tw. (7)

9 bethkis*.tw. (0)

10 bralifex*.tw. (0)

11 bramicil*.tw. (0)

12 bramitob*.tw. (2)

13 bridul*.tw. (0)

14 brulamycin*.tw. (0)

15 colther*.tw. (0)

16 dartobcin*.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

17 eltol*.tw. (0)

18 eyebrex*.tw. (0)

19 fotex*.tw. (0)

20 fytobra*.tw. (0)

21 gernebcin*.tw. (0)

22 gotabiotic*.tw. (0)

23 ibrex*.tw. (0)

24 ikobel*.tw. (0)

25 kitabis*.tw. (0)

26 mytob*.tw. (0)

27 mytocin*.tw. (0)

28 nebacin*.tw. (0)

29 nebcin*.tw. (0)

30 nebic*.tw. (2)

31 nebris*.tw. (1)

32 nutob*.tw. (0)

33 tobsin*.tw. (0)

34 ocubrax*.tw. (0)

35 ocumicin*.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

36 ocuracin*.tw. (0)
37 ramitop*.tw. (0)
38 "Rui Nuo Sai".tw. (0)
39 "Tai Tuo".tw. (0)
40 "Tai Xing".tw. (0)
41 "Tuo Xin".tw. (0)
42 tenebra*.tw. (3)
43 tirselon*.tw. (0)
44 tobacin*.tw. (0)
45 tobel*.tw. (2)
46 tober*.tw. (22)
47 tobi*.tw. (191)
48 tobra*.tw. (357)
49 tobrex*.tw. (2)
50 tobril*.tw. (3)
51 tofib*.tw. (0)
52 toravin*.tw. (0)
53 trazil*.tw. (0)
54 tronamycin*.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

55 tuberbut*.tw. (0)
56 vantobra*.tw. (0)
57 zoteon*.tw. (0)
58 pulbronkal*.tw. (0)
59 distobram*.tw. (0)
60 tomycin*.tw. (0)
61 zerodiar*.tw. (0)
62 vistadex*.tw. (0)
63 Tobramycin/ (0)
64 Aminoglycosides/ (0)
65 aminoglycosid*.tw. (1100)
66 tobyrne.tw. (0)
67 belbarmicina*.tw. (0)
68 "Bideon Biotic".tw. (0)
69 bioptic*.tw. (68)
70 consac*.tw. (5)
71 defy*.tw. (191)
72 cromycin*.tw. (0)
73 distobram*.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

74 dilaterol*.tw. (0)
75 eotob*.tw. (0)
76 eyetobrin*.tw. (0)
77 glytob*.tw. (0)
78 intob*.tw. (1)
79 isenia*.tw. (0)
80 klonamicin*.tw. (0)
81 mdas*.tw. (114)
82 micitrex*.tw. (0)
83 monobracin*.tw. (0)
84 monotobrin*.tw. (0)
85 obra*.tw. (30)
86 obry*.tw. (4)
87 ocusyn*.tw. (0)
88 ocutob*.tw. (0)
89 oftalbrax*.tw. (0)
90 oftamycin*.tw. (0)
91 poentobral*.tw. (0)
92 promisesin*.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

93 radina*.tw. (0)

94 "Xao T".tw. (0)

95 "Jia Nuo Tai".tw. (0)

96 (thilo-micine or thilomicine).tw. (0)

97 thilomaxine*.tw. (0)

98 tobro*.tw. (0)

99 tobazon*.tw. (0)

100 toflamixina*.tw. (0)

101 tomycin*.tw. (0)

102 toracin*.tw. (0)

103 notrix*.tw. (0)

104 ocle*.tw. (0)

105 verbram*.tw. (0)

106 xibrax*.tw. (0)

107 xolof*.tw. (0)

108 bronchiect*.tw. (791)

109 bronchoeect*.tw. (0)

110 (kartagener* adj4 syndrome*).tw. (39)

111 (cilia* adj4 dyskines*).tw. (130)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

112 bronch* adj4 dilat*.tw. (93)

113 young* adj syndrome*.tw. (1)

114 exp Bronchiectasis/ (0)

115 Ciliary Motility Disorders/ (0)

116 or/1-107 (2004)

117 or/108-115 (969)

118 116 and 117 (5)

119 Animals/ not (Animals/ and Humans/) (5)

120 118 not 119 (5)

121 120 (5)

122 limit 121 to english language (5)

Database: Embase

Platform: Ovid


Search date: 12/12/2016

Number of results retrieved: 91

Search strategy:

1 "47663".tw. (17)

2 "l 47663".tw. (0)
3 ("nebramycin factor 6" or "nebramycin factor VI").tw. (8)

4 aktob*.tw. (26)

5 ak-tob*.tw. (1)

6 alveoterol*.tw. (0)

7 artobin*.tw. (0)

8 bactob*.tw. (65)

9 belbarmicina*.tw. (0)

10 "Bideon Biotic".tw. (0)

11 bethkis*.tw. (7)

12 bioptic*.tw. (2511)

13 bralifex*.tw. (0)

14 bramicil*.tw. (0)

15 bramitob*.tw. (64)

16 bridul*.tw. (0)

17 brulamycin*.tw. (32)

18 colther*.tw. (3)

19 consac*.tw. (9)

20 cromycin*.tw. (1)

21 distobram*.tw. (2)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

41 mytob.tw. (1)
42 monobracin.tw. (0)
43 mdas.tw. (949)
44 monotobrin.tw. (0)
45 mytocin.tw. (0)
46 nebacin.tw. (2)
47 nebcin.tw. (542)
48 nebic-tw. (62)
49 nebris.tw. (3)
50 nutob.tw. (0)
51 notrix.tw. (0)
52 obra-tw. (603)
53 obry-tw. (25)
54 ocubrax.tw. (2)
55 ocumicin-tw. (0)
56 ocuracin-tw. (0)
57 ocusyn-tw. (0)
58 ramitop-tw. (0)
59 oftalbrax-tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

79 tobra*.tw. (8729)
80 tobrex*.tw. (191)
81 tobri*.tw. (21)
82 tobro*.tw. (14)
83 tobsin*.tw. (0)
84 toflamixina*.tw. (0)
85 tomycin*.tw. (9)
86 tofib*.tw. (10)
87 toravin*.tw. (0)
88 trazil*.tw. (2)
89 tronamycin*.tw. (0)
90 tuberbut*.tw. (0)
91 vantobra*.tw. (5)
92 zoteon*.tw. (0)
93 "Xao T".tw. (0)
94 pulbronkal*.tw. (0)
95 distobram*.tw. (2)
96 tomycin*.tw. (9)
97 zerediar*.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

98 tobryne*.tw. (0)

99 vistadex*.tw. (0)

100 *tobramycin/ (10617)

101 verbram*.tw. (0)

102 *tobramycin sulfate/ (164)

103 xolof*.tw. (0)

104 xibrax*.tw. (0)

105 isenia.tw. (0)

106 ocle*.tw. (7)

107 or/1-106 (22613)

108 (cilia* adj4 dyskines*).tw. (1630)

109 (bronch* adj4 dilat*).tw. (1465)

110 (young* adj syndrome*).tw. (86)

111 (kartagener* adj4 syndrome*).tw. (846)

112 exp bronchiectasis/ (16841)

113 bronchoect*.tw. (48)

114 bronchiect*.tw. (11683)

115 or/108-114 (20802)

116 107 and 115 (175)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

117 nonhuman/ not human/ (3710914)

118 116 not 117 (172)

119 limit 118 to (conference abstract or conference paper or conference proceeding or "conference review") (40)

120 118 not 119 (132)

121 limit 120 to english language (91)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED

Platform: Wiley

Version:

CDSR – 2005 to 7 December 2016

DARE – 1 of 4, April 2015 (legacy database)

CENTRAL – November 2016

HTA – 4th quarter 2016

NHS EED – 1 of 4, April 2015 (legacy database)

Search date: 14 December 2016

Number of results retrieved: Total – 24, as follows: CDSR: 15; DARE: 0; CENTRAL 9; HTA 0 ; NHS EED 0.

Search strategy:

1 "47663".tw. (1)

2 "I 47663".tw. (0)
3 ("nebramycin factor 6" or "nebramycin factor VI").tw. (0)

4 aktob*.tw. (1)

5 ak-tob*.tw. (0)

6 alveoterol*.tw. (0)

7 artobin*.tw. (0)

8 bactob*.tw. (6)

9 bethkis*.tw. (0)

10 bralifex*.tw. (0)

11 bramicil*.tw. (0)

12 bramitob*.tw. (12)

13 bridul*.tw. (0)

14 brulamycin*.tw. (0)

15 colther*.tw. (0)

16 dartobcin*.tw. (0)

17 eltol*.tw. (0)

18 eyebrex*.tw. (0)

19 fotex*.tw. (0)

20 fytobra*.tw. (0)

21 gernebcin*.tw. (2)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

22 gotabioc*.tw. (0)
23 ibrex*.tw. (0)
24 ikobel*.tw. (0)
25 kitabis*.tw. (0)
26 mytob*.tw. (0)
27 mytocin*.tw. (3)
28 nebacin*.tw. (0)
29 nebcin*.tw. (1)
30 nebic*.tw. (6)
31 nebris*.tw. (0)
32 nutob*.tw. (0)
33 obra*.tw. (21)
34 ocubrax*.tw. (0)
35 ocumicin*.tw. (0)
36 ocuracin*.tw. (0)
37 ramitop*.tw. (0)
38 "Rui Nuo Sai".tw. (0)
39 "Tai Tuo".tw. (0)
40 "Tai Xing".tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

41 "Tuo Xin".tw. (0)
42 tenebra*.tw. (0)
43 tirselon*.tw. (0)
44 tobacin*.tw. (0)
45 tobel*.tw. (1)
46 tober*.tw. (4)
47 tobi*.tw. (199)
48 tobra*.tw. (1137)
49 tobrex*.tw. (11)
50 tobri*.tw. (0)
51 tofib*.tw. (0)
52 toravin*.tw. (0)
53 trazil*.tw. (0)
54 tronamycin*.tw. (0)
55 tuberbut*.tw. (0)
56 vantobra*.tw. (4)
57 zoteon*.tw. (0)
58 pulbronkal*.tw. (0)
59 distobram*.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

79 micitrex*.tw. (0)

80 monobracin*.tw. (0)

81 monotobrin*.tw. (0)

82 obry*.tw. (8)

83ocusyn*.tw. (0)

84 ocutob*.tw. (0)

85 oftalbrax*.tw. (0)

86 oftamycin*.tw. (0)

87 poentobral*.tw. (0)

88 promesin*.tw. (0)

89 radina*.tw. (0)

90 "Xao T".tw. (0)

91 "Jia Nuo Tai".tw. (0)

92 (thilo-micine or thilomicine).tw. (0)

93 thilomaxine*.tw. (0)

94 tobro*.tw. (1)

95 tobazon*.tw. (0)

96 toflamixina*.tw. (0)

97 tomycin*.tw. (0)
Non-cystic fibrosis bronchiectasis: inhaled tobramycin (ES12)

98 toracin*.tw. (0)

99 notrix*.tw. (0)

100 tobsin*.tw. (0)

101 verbram*.tw. (0)

102 xibrax*.tw. (0)

103 xolof*.tw. (0)

104 ocle*.tw. (0)

105 aminoglycosides.kw. (43)

106 tobramycin.kw. (143)

107 obra*.kw. (2)

108 bronchiect*.tw. (626)

109 bronchoect*.tw. (18)

110 (kartagener* adj4 syndrome*).tw. (14)

111 (cilia* adj4 dyskines*).tw. (61)

112 (bronch* adj4 dilat*).tw. (96)

113 (young* adj syndrome*).tw. (4)

114 (ciliar* adj4 motility).tw. (11)

115 kartagener syndrome.kw. (1)

116 ciliary motility disorders.kw. (0)
Clinicaltrials.gov searches

Search date: 12/12/2016

Number of results retrieved:

Search strategies

All the searches use tobramycin and variants as the intervention and bronchiectasis as the population and are limited to clinical trials in phases 2-4.

bronchiectasis AND tobramycin – 4 results

bramitob OR brulamycin OR colther OR distobram OR eyebrex OR eyetobrin OR gernebcin OR ikobel OR monobracin OR monotobrin OR nebcina OR nebcine AND bronchiectasis – 4 results (see below)

tobra gobens OR tobra-gobens OR tobra laf OR tobrabact OR tobra-cell OR tobra cell OR tobracil OR tobradistin OR tobra-gobens OR tobrazi OR tobrexan OR tobridavi OR tobrosopt OR tomycin OR zerodiar OR artobin OR bralifex AND bronchiectasis – 0 results
tobrastill OR tobravisc OR tobrimin OR tobrin OR tobrineb OR tobrinex OR tobrsalex OR tomycin OR toravin OR trazil OR trazil ofteno OR tronamycin OR vantobra OR tobramycin vvb AND bronchiectasis – 0 results

ak-tob OR kitabis OR kitabis pak OR nebicin OR "nebramycin factor 6" OR "nebramycin factor VI" OR obracine OR tobracin OR tomycine AND bronchiectasis – 4 results (see below)

"isotic tobryne" OR tobryne OR "I 47663" OR nebacin OR "nebcin paediatric" OR "nebcin pediatric" OR nebicina OR ocumicin OR ocuracin OR tenebra OR tirselon OR tobacin OR tobralex AND bronchiectasis – 4 results (see below)

"tobi nextgen" OR "tobi podhaler" AND bronchiectasis – 4 results (see below)

tobramaxin OR tobramicin OR tobramicina OR tobramycine OR tobral OR dartobcin OR toberan OR tobra OR "tobramycin sulphate" OR "tobramycin sulfate" OR tobraneg OR tobrasix OR ocumicin AND bronchiectasis – 4 results (see below)

tobrineb OR cromycin OR tobradact OR tobrazid OR thilo-micine OR bramcil OR nebris OR distobran OR oftamycin OR promesin OR tobrased OR defy OR tenebra OR tobrex AND bronchiectasis – 4 results

**Development of this evidence summary**

The evidence summary: process guide (2017) sets out the process NICE uses to select topics for evidence summaries and details how the summaries are developed, quality assured and approved for publication.

**Expert advisers**

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**Declarations of interest**

Anastasios Lekkas: No interests declared.

Andrew Jones: Is a member of the NHS England respiratory specialist clinical reference group, a trustee of the UK CF Trust and a member of NICE clinical guideline committee for cystic fibrosis.

Rowland Bright-Thomas: No interests declared.

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**About this evidence summary**

Evidence summaries provide a summary of the best available published evidence for selected new medicines, unlicensed medicines or off-label use of licensed medicines.

The summaries assess the strengths and weaknesses of the best available evidence to inform health professionals and commissioners' decision-making.

This summary is not NICE guidance.

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