NICE advice

Non-cystic fibrosis bronchiectasis: colistimethate sodium

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in January 2014. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Colistimethate sodium (Colobreathe, Colomycin injection and Promixin) is licensed for treating pulmonary infections caused by *Pseudomonas aeruginosa* in people with cystic fibrosis but not in non-cystic fibrosis bronchiectasis. Four small case series (total n=148) provide weak evidence for the effectiveness of nebulised colistimethate sodium (Colomycin injection and Promixin) in people with non-cystic fibrosis bronchiectasis and *P. aeruginosa*. Nebulised or inhaled colistimethate sodium is very commonly associated with adverse respiratory effects, including cough, dyspnoea, bronchospasm and sore throat.

Regulatory status: off-label. The manufacturer of Promixin, Profile Pharma, has indicated that it plans to apply for a UK marketing authorisation for nebulised colistimethate sodium for treating chronic *P. aeruginosa* infection within 2–3 years.

The topic was prioritised because there was a high volume of requests from the NHS for information on this topic and there is uncertainty about the balance of risks and benefits when colistimethate sodium is used for non-cystic fibrosis bronchiectasis.

Effectiveness	Safety
• Out of 3 similar case series, 2 found that nebulised colistimethate sodium statistically significantly reduced the mean number of exacerbations. The third did not look at this outcome. • Out of the 3 case series, 1 found that treatment statistically significantly reduced the mean number of hospital admissions. The 2 others found no significant difference. • All 3 case series found that treatment had no significant effect on forced expiratory volume in 1 second (FEV_1). However, 1 of the 3 case series found that treatment statistically significantly reduced the annual decline in FEV_1 and forced vital capacity (FVC). • A fourth study found no significant differences in the mean number of hospital admissions, duration of hospital stay, or duration of antibiotic use between nebulised colistimethate sodium and nebulised tobramycin.	• Out of 3 similar case series, 2 did not report on adverse events. The third study reported that there were no adverse events. • A fourth study reported that there was no significant difference between nebulised colistimethate sodium and nebulised tobramycin in drug-related adverse events or withdrawals because of adverse events. • The summary of product characteristics for Promixin states that acquired resistance to colistimethate sodium by *P. aeruginosa* has been reported during clinical use.

Patient factors	Resource implications
• The most common adverse effects of nebulised or inhaled colistimethate sodium are cough, dyspnoea, bronchospasm and sore throat (affecting at least 1 in 10 people). • In 1 study, 3 out of 30 patients did not receive nebulised colistimethate sodium because of intolerance. • Some people may find it difficult or inconvenient to use a nebuliser. • Some people may prefer to use an inhaler. However, all of the case series used nebulised colistimethate sodium. No case series used the colistimethate sodium dry powder inhaler (Colobreathe).	• Colobreathe costs £968.80 for 56 capsules (containing 1.6625 million units) and a Turbospin inhaler. • Colomycin injection costs £18.00 for 10 vials containing 1 million units of colistimethate sodium and £32.00 for 10 vials containing 2 million units of colistimethate sodium. • Promixin costs £138.00 for 30 vials containing 1 million units of colistimethate sodium. The price includes the cost of the nebuliser, training, support service and all related consumables.

Key points

This evidence summary outlines the evidence for nebulised or inhaled colistimethate sodium for treating non-cystic fibrosis bronchiectasis.

Colistimethate sodium is a polymyxin antibiotic with activity against gram negative bacteria including *P. aeruginosa*. Colistimethate sodium powder for nebuliser solution (Colomycin injection, 1 or 2 million international units or Promixin, 1 million international units) is licensed for treating pulmonary infections caused by *P. aeruginosa* in people with cystic fibrosis. A dry powder inhaler (Colobreathe, 1.6625 million international units) is also licensed for the treatment of chronic pulmonary infections caused by *P. aeruginosa* in those aged 6 years and over with cystic fibrosis. Use of nebulised or inhaled colistimethate sodium for treating non-cystic fibrosis bronchiectasis is off-label.

No published randomised controlled trials (RCTs) have investigated nebulised or inhaled colistimethate sodium for non-cystic fibrosis bronchiectasis. Four small case series were identified that reported outcomes in a total of 148 people with non-cystic fibrosis bronchiectasis and *P. aeruginosa* colonisation who received nebulised colistimethate sodium.

Three of the case series (White et al. 2012, n=30; Dhar et al. 2010, n=19; and Steinfort and Steinfort 2007, n=18) used historical self-controls to compare outcomes before and after treatment with nebulised colistimethate sodium. Two of these case series found that treatment statistically significantly reduced the mean number of exacerbations (from 3.93 to 2.09 per year [p<0.002] in White et al. 2012 and from 7.8 to 2.7 per year [p<0.001] in Dhar et al. 2010). The third case series did not report exacerbations. White et al. 2012 and Steinfort and Steinfort 2007 found that treatment had no significant effect on hospital admissions, but Dhar et al. 2010 found that treatment statistically significantly reduced the mean number of hospital admissions (from 3.0 to 0.95 per year, p=0.002).

Two of the case series (White et al. 2012 and Dhar et al. 2010) found that treatment had no significant effect on FEV_1. The third case series (Steinfort and Steinfort 2007) also found that treatment had no significant effect on FEV_1 or FVC. However, it found that treatment statistically significantly reduced the annual decline in FEV_1 (from 104 ml per year before treatment to 44 ml after treatment, p=0.035) and FVC (from 110 ml per year before treatment to 48 ml after treatment, p=0.033).

The fourth case series (Berlana et al. 2011, n=81) compared post-treatment outcomes in people who had received nebulised colistimethate sodium alone, tobramycin alone or both. There were no significant differences in the mean number of hospital admissions, duration of hospital stay, or duration of antibiotic use between colistimethate sodium and tobramycin. Combination treatment significantly reduced these outcomes compared with tobramycin alone.

White et al. (2012) and Dhar et al. (2010) did not report adverse events, and Steinfort and Steinfort (2007) reported that there were no adverse events. In Berlana et al. (2011), drug-related adverse events were reported by 58% of people who took colistimethate sodium, most commonly dyspnoea (shortness of breath), bronchospasm and cough (each affecting 12% of patients), wheezing (10%) and dry mouth (6%). There was no significant difference between colistimethate sodium and tobramycin in drug-related adverse events or withdrawals because of adverse events.

According to the summaries of product characteristics, colistimethate sodium is very commonly associated with adverse respiratory effects (affecting at least 1 in 10 people) including cough, dyspnoea, bronchospasm and sore throat. The summary of product characteristics for Promixin states that there have been reports of *P. aeruginosa* acquiring resistance to colistimethate sodium during clinical use.

The 4 case series provide weak evidence for the safety and effectiveness of nebulised colistimethate sodium for treating non-cystic fibrosis bronchiectasis and colonisation with *P.*

aeruginosa. One unpublished RCT, Inhaled Promixin in the treatment of non-cystic fibrosis bronchiectasis, has now been completed and, once fully published and peer-reviewed, may provide higher level evidence about the safety and efficacy of nebulised colistimethate sodium for treating non-cystic fibrosis bronchiectasis.

About this evidence summary

'Evidence summaries: unlicensed or off-label medicines' summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, **but this summary is not NICE guidance.**

Overview for healthcare professionals

Regulatory status of colistimethate sodium

Colistimethate sodium powder for nebuliser solution is licensed for treating pulmonary infections caused by *Pseudomonas aeruginosa* in people with cystic fibrosis. It is available as Colomycin injection (1 or 2 million international units) and Promixin (1 million international units). A dry powder inhaler (Colobreathe, 1.6625 million international units) is also licensed for treating chronic pulmonary infections caused by *P. aeruginosa* in people with cystic fibrosis, but only in people aged 6 years or older.

Use of nebulised or inhaled colistimethate sodium for non-cystic fibrosis bronchiectasis is off-label. In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using colistimethate sodium outside its authorised indications.

The manufacturer of Promixin, Profile Pharma, has indicated that it plans to apply for a UK marketing authorisation in 2–3 years for nebulised colistimethate sodium for treating chronic *P.*

aeruginosa infections.

Evidence statements

- No published randomised controlled trials (RCTs) have investigated nebulised or inhaled colistimethate sodium for non-cystic fibrosis bronchiectasis.
- Four case series were identified that reported use of nebulised colistimethate sodium in people with non-cystic fibrosis bronchiectasis and bronchial colonisation with *P. aeruginosa*. Two of the case series also included people with chronic obstructive pulmonary disease.
- White et al. (2012) (n=30) found that a *Pseudomonas* eradication protocol that included 3 months of nebulised colistimethate sodium (2 million units twice daily with other oral or intravenous antibiotics) statistically significantly reduced the mean number of exacerbations from 3.93 per year to 2.09 per year ($p<0.002$), but had no significant effect on hospital admissions or forced expiratory volume in 1 second (FEV_1) over a median follow-up of 26.4 months.
- Dhar et al. (2010) (n=19) found that treatment with nebulised colistimethate sodium (1–2 million units twice daily) for 6 months or more (mean 21.2 months) statistically significantly reduced the mean number of exacerbations from 7.8 per year to 2.7 per year ($p<0.001$) and the mean number of hospital admissions from 3.0 per year to 0.95 per year ($p=0.002$), but had no significant effect on FEV_1.
- Steinfort and Steinfort (2007) (n=18) found that long-term (6–116 months) treatment with nebulised colistimethate sodium (30 mg daily, around 375,000 units) had no significant effect on hospital admissions but improved some measures of lung function. Treatment had no significant effect on FEV_1 or forced vital capacity (FVC) but reduced the annual decline in FEV_1 (from 104 ml per year to 44 ml per year, $p=0.035$) and FVC (from 110 ml per year to 48 ml per year, $p=0.033$). A significant improvement in quality of life on a visual analogue scale was seen after colistimethate sodium treatment (score 3.6 before treatment and 6.2 after treatment, $p=0.001$). However, the scale used has not been validated.
- Berlana et al. (2011) (n=81) compared post-treatment outcomes in people who received nebulised colistimethate sodium alone (1–2 million units twice daily), tobramycin alone, or both for 3 months or more. There were no significant differences in the mean number of hospital admissions, duration of hospital stay or duration of antibiotic use between colistimethate sodium and tobramycin. Combination treatment reduced these outcomes compared with tobramycin alone.

- White et al. (2012) and Dhar et al. (2010) did not report on adverse events, and Steinfort and Steinfort (2007) reported that there were no adverse events. In Berlana et al. (2011), drug-related adverse events were reported by 58% of people who took colistimethate sodium, most commonly dyspnoea (shortness of breath), bronchospasm and cough (each affecting 12% of patients), wheezing (10%) and dry mouth (6%). There was no significant difference between colistimethate sodium and tobramycin in drug-related adverse events or withdrawals because of adverse events.

- According to the summaries of product characteristics, colistimethate sodium is very commonly associated with adverse respiratory effects (affecting at least 1 in 10 people), including cough, dyspnoea, bronchospasm and sore throat. The summary of product characteristics for Promixin states that there have been reports of *P. aeruginosa* acquiring resistance to colistimethate sodium during clinical use.

- The 4 case series provide weak evidence for the safety and effectiveness of nebulised colistimethate sodium for treating non-cystic fibrosis bronchiectasis and colonisation with *P. aeruginosa*.

- One randomised controlled trial, Inhaled Promixin in the treatment of non-cystic fibrosis bronchiectasis, has been completed but not yet published. Once published and peer-reviewed, this may provide higher level evidence about the safety and efficacy of nebulised colistimethate sodium for treating non-cystic fibrosis bronchiectasis.

Summary of the evidence

This section gives a brief summary of the main evidence. A more thorough analysis is given in the Evidence review section.

Efficacy

Table 1 provides a summary of the 3 case series (White et al., Dhar et al. and Steinfort and Steinfort) that used historical self-controls to compare outcomes before and after treatment with nebulised colistimethate sodium.

The case series by Berlana et al. (2011) (n=81) is not compatible with the 3 case series included in table 1, because it compared the post-treatment outcomes of 3 treatment groups (nebulised colistimethate sodium alone, colistimethate sodium plus tobramycin, or tobramycin alone), rather than comparing outcomes before and after treatment with nebulised colistimethate sodium.

Berlana et al. (2011) found no significant differences between colistimethate sodium alone and

tobramycin alone in the mean number of hospital admissions, duration of hospital stay, or duration of antibiotic use in people with non-cystic fibrosis bronchiectasis or chronic obstructive pulmonary disease with *P. aeruginosa* bronchial colonisation. Compared with tobramycin alone, the combination of colistimethate sodium and tobramycin was associated with a significant reduction in hospital admissions (0.4 compared with 1.9 per person per year, $p<0.05$), duration of hospitalisation (2.8 days compared with 22.5 days per person per year, $p<0.05$), and duration of antibiotic use (2.0 days compared with 14.8 days per person per year, $p<0.05$). Reliable lung function measures were available for only 32% (31/97) of all treatment courses.

Table 1 Summary of the case series

	Before treatment	After treatment	Analysis (before to after treatment difference)
White et al. (2012)			
Patients	30 people with non-cystic fibrosis bronchiectasis who received *Pseudomonas* eradication therapy that included nebulised colistimethate sodium (2 million units twice daily for 3 months)		
Outcomes			
Pseudomonas eradication from sputum	Not applicable	80% (24/30)	54% (13/24) remained *Pseudomonas*-free at their latest follow-up (median 14.3 months) 46% (11/24) subsequently re-cultured *Pseudomonas* (median time to re-infection 6.2 months)
Exacerbations (mean)	3.93 per year	2.09 per year	$p<0.002$
Hospital admissions (mean)	0.39 per year	0.29 per year	NS, p value not reported
Lung function (mean percentage predicted)	FEV_1 62.1%	FEV_1 64.1%	NS, p value not reported
Safety	NR	NR	Adverse events were not reported. 10% (3/30) withdrew because of intolerance to colistimethate sodium

Dhar et al. (2010)			
Patients	19 people with non-cystic fibrosis bronchiectasis and *Pseudomonas* colonisation who received nebulised colistimethate sodium (1–2 million units twice daily) for at least 6 months (mean 21.2 months)		
Outcomes			
Pseudomonas-positive sputum samples (mean)	4.2 per year	0.5 per year	p<0.001
Exacerbations (mean)	7.8 per year	2.7 per year	p<0.001
Hospital admissions (mean)	3.0 per year	0.95 per year	p=0.002
Lung function (mean)	FEV_1 1.13 litres	FEV_1 1.14 litres	NS, p value not reported
Safety	NR	NR	Adverse events were not reported
Steinfort and Steinfort (2007)			
Patients	18 people with non-cystic fibrosis bronchiectasis or severe COPD and chronic bronchial sepsis who received nebulised colistimethate sodium (30 mg daily, around 375,000 units) long term (6 to 116 months)		
Outcomes			
Hospital admissions[1]	1.1 per year	0.84 per year	p=0.493 NS
Lung function[1]	FEV_1 1.07 litres	FEV_1 1.02 litres	p=0.400 NS
	FVC 2.0 litres	FVC 1.9 litres	p=0.295 NS
Lung function (annual decline)	FEV_1 104 ml per year	FEV_1 44 ml per year	p=0.035

	FVC 110 ml per year	FVC 48 ml per year	p=0.033
Quality of life (VAS)	3.6	6.2	p=0.001
Safety	NR	NR	Reported that there were no adverse events
Abbreviations: COPD, chronic obstructive pulmonary disease; NR, not reported; NS, non-significant; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; p, p value; VAS, visual analogue scale (not validated). [1] These are assumed to be mean values, although this is not stated in the paper.			

Safety

According to the summaries of product characteristics, colistimethate sodium (Colomycin injection and Promixin powder for nebuliser solution, and Colobreathe dry powder for inhalation) is very commonly associated with adverse respiratory effects (affecting at least 1 in 10 people) including cough, dyspnoea (shortness of breath), bronchospasm and sore throat. Colobreathe also very commonly (in at least 1 in 10 people) causes dysphonia (hoarseness and difficultly speaking) and dysgeusia (distorted taste). It is also associated (in at least 1 in 100 people) with nausea and vomiting, tinnitus, balance disorder, headache, arthralgia and fatigue.

The case series Dhar et al. (2010) and White et al. (2012) did not report adverse events. Steinfort and Steinfort (2007) reported that there were no adverse events in the 18 people who received long-term nebulised colistimethate sodium.

In Berlana et al. (2011) drug-related adverse events were experienced by 58% of people (29/50) who took colistimethate sodium alone and 28% of people (20/72) who took tobramycin alone (no significant difference, p=0.24). There was no significant difference between the colistimethate sodium and tobramycin groups in the number of withdrawals because of adverse events (26% with colistimethate sodium compared with 13% with tobramycin, p=0.06). The most common adverse events seen with colistimethate sodium were shortness of breath, bronchospasm and cough (each affecting 6/50 patients, 12%), wheeze (5/50, 10%) and dry mouth (3/50, 6%).

Cost effectiveness and cost

According to MIMS (November 2013), the costs of preparations of colistimethate sodium for inhalation (excluding VAT) are as follows:

- Colobreathe costs £968.80 for 56 capsules containing 1.6625 million units and a Turbospin inhaler.
- Colomycin injection costs £18.00 for 10 vials containing 1 million units of colistimethate sodium and £32.00 for 10 vials containing 2 million units of colistimethate sodium.
- Promixin costs £138.00 for 30 vials containing 1 million units of colistimethate sodium. The price includes the cost of the nebuliser, training, support service and all related consumables.

Relevance to NICE guidance programmes

This evidence summary reviews the use of nebulised or inhaled colistimethate sodium for treating non-cystic fibrosis bronchiectasis. NICE has also issued guidance on Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (NICE technology appraisal guidance 276).

Intervention and alternatives

Colistimethate sodium is a polymyxin antibiotic that is active against gram negative bacteria including *Pseudomonas aeruginosa*, *Acinetobacter baumannii* and *Klebsiella pneumoniae*. It is not absorbed when given orally.

Inhaled colistimethate sodium is licensed for treating pulmonary infections caused by *P. aeruginosa* in people with cystic fibrosis. The following preparations are available:

- Colobreathe dry powder for inhalation using the Turbospin inhaler. Each capsule contains 1.6625 million international units, equivalent to 125 mg of colistimethate sodium. This preparation is licensed only for chronic pulmonary infections in people aged 6 years and older.
- Colomycin injection powder for solution for inhalation using a nebuliser. Each vial contains 1 or 2 million international units of colistimethate sodium (dose equivalent not specified).
- Promixin powder for nebuliser solution. Each vial contains 1 million international units, equivalent to 80 mg colistimethate sodium.

There are currently no licensed colistimethate products for the treatment of non-cystic fibrosis bronchiectasis. However, the manufacturer of Promixin, Profile Pharma, has indicated that it intends to apply for a UK marketing authorisation within 2–3 years for nebulised colistimethate sodium for treating chronic *P. aeruginosa* infection.

In clinical practice, colistimethate is reportedly used in a similar way for non-cystic fibrosis bronchiectasis caused by *P. aeruginosa* to how it is used in people with cystic fibrosis. The limitations of the evidence for this use are discussed in the evidence review section. NICE guidance on Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis recommends colistimethate sodium dry powder for inhalation (Colobreathe) as an option for treating chronic pulmonary infection caused by *P. aeruginosa* in people with cystic fibrosis only if:

- they would clinically benefit from continued colistimethate sodium but do not tolerate it in its nebulised form (Colomycin injection or Promixin) and thus tobramycin therapy would otherwise be considered **and**
- the manufacturer provides colistimethate sodium dry powder for inhalation with the discount agreed as part of the patient access scheme to primary, secondary and tertiary care in the NHS.

When used for its licensed indication in adults and children older than 2 years, the recommended dose of nebulised colistimethate sodium is 1 to 2 million international units 2 to 3 times daily, depending on the preparation (Colomycin injection or Promixin). Colomycin may be used at a lower dose in children younger than 2 years. The recommended dose of colistimethate sodium dry powder for inhalation (Colobreathe) for adults and children older than 6 years is 1 capsule for inhalation twice daily using the Turbospin inhaler.

Condition

The lungs have a sophisticated defence mechanism to maintain sterility. However, if this is breached they become susceptible to infection, colonisation (the persistence of bacteria in the lower respiratory tract) can occur, and subsequent inflammation can cause airway damage and further impair the lungs' defences. The British Thoracic Society guideline for non-CF bronchiectasis defines bronchiectasis as persistent or recurrent bronchial sepsis related to irreversibly damaged and dilated bronchi. Many disease processes can result in bronchiectasis, including previous pneumonia or other lower respiratory tract infection, immune deficiency (particularly in children), congenital airway abnormality and aspiration injury (foreign body, gastrointestinal contents or noxious gases) but often the cause is unknown.

Symptoms of bronchiectasis can vary from intermittent episodes of expectoration related to localised infection in the affected region of the lung, to persistent daily expectoration of large volumes of purulent sputum. There may be other non-specific respiratory symptoms, including shortness of breath, chest pain and haemoptysis.

Some organisms, for example *P. aeruginosa*, can be difficult to eradicate if they colonise the lower respiratory tract in people with bronchiectasis. Colonisation with *P. aeruginosa* is associated with worse symptoms and quality of life scores than colonisation with other bacteria and may lead to accelerated decline in forced expiratory volume in 1 second (FEV_1).

Alternative treatment options

The aims of treatment for non-cystic fibrosis bronchiectasis are to maintain or improve lung function by identifying and treating any underlying cause; to reduce exacerbations, control symptoms and improve quality of life; and, in children, to achieve normal growth and development. Treatments may include airway clearance using physiotherapy, pulmonary rehabilitation, antibiotics, bronchodilators (beta-2 agonists and anticholinergics) and surgery. There is little evidence to support using inhaled corticosteroids (except in people with comorbid asthma) or mucolytics, and no evidence to support the routine use of oral corticosteroids or leukotriene receptor antagonists in people with bronchiectasis.

The British Thoracic Society guideline for non-CF bronchiectasis recommends that antibiotics 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) and/or systemic illness. Sputum culture is recommended to guide antibiotic therapy: empirical antibiotics should be given until the results are known. The first-line treatment is generally amoxicillin or clarithromycin (in people who are allergic to penicillin) for 14 days.

The British Thoracic Society guideline for non-CF bronchiectasis recommends oral ciprofloxacin for people with confirmed *P. aeruginosa* infection. However, the guideline notes that there is a significant chance of antibiotic resistance, with poor clinical response, after repeated courses of quinolones. The guideline states that if there is no response to oral ciprofloxacin, monotherapy with an appropriate intravenous antibiotic should be considered. It also recommends that, to reduce the development of drug resistance, combination antibiotic therapy should be considered for infections caused by strains of *P. aeruginosa* that are resistant to 1 or more antipseudomonal antibiotics (including ciprofloxacin) or if the clinician suspects the person will need many subsequent antibiotic courses. It outlines strategies for eradicating *P. aeruginosa* from the sputum of people with cystic fibrosis and notes that individual clinicians will decide which and how aggressive a strategy to use in people with non-cystic fibrosis bronchiectasis.

The British Thoracic Society 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. It also advises using long-term nebulised antibiotics (gentamicin, tobramycin or colistimethate sodium) in people who have chronic *P. aeruginosa* infection, with the choice of antibiotic guided by the results of tests for antibiotic sensitivity. The British Thoracic Society notes that further studies are needed to address the optimal antibiotic choice and doses.

When nebulised antibiotic treatment is used, the British Thoracic Society advises that a multidisciplinary team that includes a chest physician, physiotherapist and respiratory nurse should coordinate care; that the person should receive ongoing support once treatment is started; and that compressors and nebulisers that meet performance and safety standards should be used. See the European Respiratory Society's guidelines on nebuliser treatment.

Evidence review: efficacy

No published randomised controlled trials (RCTs) have investigated nebulised or inhaled colistimethate sodium for treating non-cystic fibrosis bronchiectasis.

Four case series were identified that reported using nebulised colistimethate sodium in people with non-cystic fibrosis bronchiectasis and bronchial colonisation with *Pseudomonas aeruginosa*. Three of the case series (White et al. 2012, n=30; Dhar et al. 2010, n=19; and Steinfort and Steinfort 2007, n=18) used historical self-controls to compare outcomes before and after treatment with nebulised colistimethate sodium. The fourth case series (Berlana et al. 2011, n=81) compared post-treatment outcomes in people who had received nebulised colistimethate sodium alone, tobramycin alone or both.

White et al. (2012)

To assess the outcomes of treatment, White et al. (2012) retrospectively identified all people (n=30) with non-cystic fibrosis bronchiectasis who had received '*Pseudomonas* eradication therapy' at the Royal United Hospital, Bath, between January 2004 and January 2010. The mean age of the patients was 62.2 years. The cause of bronchiectasis was earlier infection in 13 people, connective tissue disease in 3 people, and unknown in 14 people. Associated conditions included chronic obstructive pulmonary disease (COPD, 6 people), asthma (5 people) and allergic bronchopulmonary aspergillosis (3 people).

The decision to start treatment usually followed 2 sputum cultures that were positive for *P. aeruginosa* (range 1 to 9, median time from first culture to treatment 7.2 months). The *Pseudomonas* eradication protocol was:

- intravenous regimen: gentamicin (4 mg/kg) plus ceftazidime (2 g 3 times daily) for 2 weeks, followed by nebulised colistimethate sodium (2 million units twice daily) for 3 months, with or without oral ciprofloxacin (500 mg twice daily) for 3 months.
- oral regimen: ciprofloxacin (500 mg twice daily) for 3 months plus nebulised colistimethate sodium (2 million units twice daily) for 3 months.

Twelve patients received intravenous antibiotics, 5 received oral ciprofloxacin, and 13 received intravenous antibiotics followed by oral ciprofloxacin. Intravenous antibiotics other than those in the protocol were used at the clinician's discretion in 8 people, mainly because of drug allergy or intolerance. Twenty-five patients also received nebulised colistimethate sodium; 5 people did not receive it because of intolerance (n=3) or because of a clinical decision (n=2).

Eradication of *Pseudomonas* was defined as a negative culture from the next sputum sample, and recurrence was defined as the first positive culture after treatment. Other outcomes included the number of exacerbations (defined as episodes of increased symptoms of bronchiectasis needing oral or intravenous antibiotics) and hospital admissions for intravenous antibiotics, and lung function (forced expiratory volume in 1 second [FEV_1]). Median follow-up was 26.4 months. The results were as follows:

- *Pseudomonas* eradication. *Pseudomonas* was initially eradicated from the sputum of 24 out of 30 patients (80%). Of these, 13 (54%) remained *Pseudomonas*-free at their latest follow-up (median 14.3 months), and 11 (46%) experienced a recurrence of *Pseudomonas* (median time to re-infection 6.2 months).
- Exacerbations. Treatment statistically significantly reduced the mean number of exacerbations needing antibiotics from 3.93 per year before treatment to 2.09 after treatment ($p<0.002$).
- Hospital admissions. Treatment did not statistically significantly reduce the mean number of admissions (0.39 per year before treatment and 0.29 per year after treatment, no significant difference).
- Lung function.Treatment also had no effect on lung function, with mean percentage predicted FEV_1 62.1% before treatment and 64.1% after treatment (no significant difference).

Dhar et al. (2010)

Dhar et al. (2010) retrospectively assessed non-cystic fibrosis bronchiectasis and colonisation with *P. aeruginosa* in people (n=19) who had received a minimum of 6 months of treatment with nebulised colistimethate sodium (1–2 million units twice daily) at the Northumbria NHS Trust.

People who had received concomitant macrolide antibiotic treatment for more than 4 weeks were excluded. The mean age of the patients was 66 years, 15 had known causes for their bronchiectasis, although these were not reported.

Outcomes included the number of hospital admissions, exacerbations that needed rescue antibiotics and had positive sputum cultures for *P. aeruginosa*, and lung function (FEV_1). The mean length of data collection before starting colistimethate sodium treatment was 23.6 months and the mean duration of treatment was 21.2 months (range 6–39 months). The results were as follows:

- *Pseudomonas* sputum positivity. Colistimethate sodium statistically significantly reduced the mean number of positive samples from 4.2 per year to 0.5 per year ($p<0.001$).
- Exacerbations. Colistimethate sodium statistically significantly reduced the mean number of exacerbations from 7.8 per year to 2.7 per year ($p<0.001$).
- Hospital admissions. Colistimethate sodium statistically significantly reduced the mean number of admissions from 3.0 per year to 0.95 per year ($p=0.002$).
- Lung function.Colistimethate sodium had no effect on lung function: mean FEV_1 was 1.13 litres before treatment and 1.14 litres after treatment (no significant difference reported).

Steinfort and Steinfort (2007)

Steinfort and Steinfort (2007) was an Australian case series that prospectively examined the effects of long-term nebulised colistimethate sodium (30 mg daily in 2 ml of saline or salbutamol solution, estimated to equate to around 375,000 units) in 18 people with either confirmed bronchiectasis or severe COPD (FEV_1 less than 40% of predicted). All patients had repeated sputum cultures that were positive for multidrug-resistant gram negative bacteria, frequent exacerbations or exacerbations needing hospital admission, poor symptom control, and production of a high volume of sputum between exacerbations. Of the 18 patients (mean age 69 years), 14 had bronchiectasis of unknown cause and 4 had severe COPD or chronic infective bronchitis; 14 had *P. aeruginosa* isolated from sputum.

Outcomes included measures of lung function, hospital admissions and quality of life (measured on a non-validated visual analogue scale). Lung function was measured on a mean of 9.4 occasions over a period ranging from 2 to 11 years before starting colistimethate sodium treatment. Once treatment started, patients were assessed regularly about every 6 months, over a period of 6–116 months. The results were as follows:

- Lung function. Three people (16.6%) were reported to show improvement in FEV_1. Overall, nebulised colistimethate sodium statistically significantly reduced the mean annual decline in FEV_1 (from 104 ml per year before treatment to 44 ml per year after treatment, p=0.035) and forced vital capacity (FVC: from 110 ml per year before treatment to 48 ml per year after treatment, p=0.033). However, it had no significant effect on FEV_1 (1070 ml before treatment and 1020 ml after treatment, p=0.400) or FVC (2.0 litres before treatment and 1.9 litres after treatment, p=0.295).

- Hospital admissions. Colistimethate sodium treatment did not significantly reduce the number of hospital admissions (1.1 per year before treatment and 0.84 per year after treatment, p=0.493).

- Quality of life. Treatment statistically significantly improved patient-reported quality of life (from 3.6 before treatment to 6.2 after treatment, p=0.001).

Berlana et al. (2011)

Berlana et al. (2011) was a Spanish case series that prospectively compared outcomes in 81 outpatients with non-cystic fibrosis bronchiectasis or COPD who received long-term (at least 12 weeks) nebulised treatment for *P. aeruginosa* bronchial colonisation between January 2004 and December 2008. Bronchial colonisation was confirmed by 3 positive sputum samples within a 6 month period. Patients were required to be symptom-free at entry.

The 81 patients received 97 courses of antibiotic treatment: 31 received nebulised colistimethate sodium (1 to 2 million units twice daily), 16 received colistimethate sodium plus tobramycin (an aminoglycoside antibiotic, which is also licensed for treating *P. aeruginosa* colonisation in people with cystic fibrosis), and 50 received tobramycin alone. The choice of treatment depended on clinical judgement. Supplementary use of oral antibiotics was permitted.

The mean age of the patients was 62.5 years. Eighty-six per cent of the courses of inhaled antibiotics (n=83) were primarily for bronchiectasis and the remainder were for COPD. There was no significant difference between the baseline characteristics of those receiving colistimethate sodium or tobramycin plus colistimethate sodium, compared with those receiving tobramycin alone.

Patients were reviewed every 6 months. Mean follow-up was 578 days. The primary outcomes were frequency and duration of hospitalisations for exacerbations. Secondary outcomes included antibiotic use during admission, changes in respiratory function, achievement of sustained *P. aeruginosa* eradication, mortality, emergence of bacterial resistance and adverse events.

There were no significant differences between colistimethate sodium alone and tobramycin alone in the mean number of hospital admissions, duration of hospital stay or duration of antibiotic use.

Compared with tobramycin alone, the combination of colistimethate sodium and tobramycin was associated with a significant reduction in hospital admissions (0.4 compared with 1.9 per person per year, $p<0.05$), duration of hospital stay (2.8 days compared with 22.5 days per person per year, $p<0.05$), and duration of antibiotic use (2.0 days compared with 14.8 days per person per year, $p<0.05$).

Reliable lung function measures were available for only 32% of the courses of treatment (31/97). No significant differences were found in the mean change per year in lung function tests between the treatment groups.

Of 29 courses of inhaled colistimethate sodium during which sputum culture was performed, *P. aeruginosa* was eradicated in 17% (n=5), colonisation was reduced in 21% (n=6), culture remained negative in 7% (n=2) and there was no response in 55% (n=16). There was no significant difference in eradication rates between the treatment groups.

Unpublished randomised controlled trial

An RCT, Inhaled Promixin in the treatment of non-cystic fibrosis bronchiectasis, has been completed but not yet published. This double-blind, multicentre RCT included 144 people with non-cystic fibrosis bronchiectasis who had had at least 2 sputum samples positive for *P. aeruginosa* within the previous 12 months and had completed treatment for an exacerbation of bronchiectasis within 21 days of screening. They were randomised to receive nebulised colistimethate sodium (1 million units per ml) or saline twice daily for up to 6 months. The primary outcome was the number of days from baseline (or first treatment dose) until the first exacerbation. Secondary outcomes included change in sputum mass and culture, change in FEV_1, quality of life, adherence and adverse events. Without a fully published version of this study, it is not possible to critically appraise it to assess how it informs practice in this area.

Evidence review: safety

Adverse effects listed in summaries of product characteristics

Colistimethate sodium (Colomycin injection and Promixin powder for nebuliser solution, and

Colobreathe dry powder for inhalation) is very commonly associated with adverse respiratory effects (affecting at least 1 in 10 people) including cough, dyspnoea (shortness of breath), bronchospasm and sore throat. Colobreathe also very commonly (in at least 1 in 10 people) causes dysphonia (hoarseness and difficultly speaking) and dysgeusia (distorted taste), and is associated (in at least 1 in 100 people) with nausea and vomiting, tinnitus, balance disorder, headache, arthralgia and fatigue.

Adverse effects in case series

White et al. (2012) did not report adverse effects. However, they stated that 3 out of 30 patients (10%) did not receive nebulised colistimethate sodium because of intolerance.

Dhar et al. (2010) did not report adverse effects. Out of the 19 patients, 2 (11%) stopped treatment, 1 in error and 1 because of lack of efficacy.

In Steinfort and Steinfort (2007), no adverse effects were reported by the 18 people who received colistimethate sodium over a period of 6–116 months. One person stopped treatment because of perceived ineffectiveness.

In Berlana et al. (2011), safety analyses were undertaken and included all people who received at least 1 day of treatment with the inhaled therapy. Drug-related adverse events were experienced by 29 out of 50 people who took colistimethate sodium alone (58%) and 20 out of 72 people who took tobramycin alone (28%). There was no significant difference in adverse events between colistimethate sodium and tobramycin (p=0.24).

There was also no significant difference in the number of withdrawals because of adverse events in the colistimethate sodium or tobramycin groups (13/50 [26%] compared with 9/72 [13%], borderline non-significant p=0.06).

Twelve patients (14.8%) died during the case series timeframe (all from respiratory causes), with no significant differences between the treatment groups.

The most common adverse events seen with colistimethate sodium were shortness of breath, bronchospasm and cough (each affecting 6/50 people, 12%), wheeze (5/50, 10%) and dry mouth (3/50, 6%).

Antimicrobial resistance

In September 2013, the Department of Health published a 5-year strategy to improve the knowledge and understanding of antimicrobial resistance and conserve and steward the effectiveness of existing treatments. This strategy has important implications for the use of antibiotics and the need for good husbandry around their use.

The British Thoracic Society guideline for non-CF bronchiectasis points out that long-term use of antibiotics may result in antibiotic resistance in individual patients and alternative antibiotics should be chosen depending on sensitivity results. According to the summary of product characteristics for Promixin, *P. aeruginosa* has been reported as acquiring resistance to colistimethate sodium during clinical use. Susceptibility testing should be performed for people who are treated on a long-term basis, at regular clinic visits and whenever the person experiences an exacerbation.

In Berlana et al. (2011), bacterial resistance developed in 8% of courses of colistimethate sodium alone (2/26), compared with 55% (18/33) of courses of tobramycin alone. Compared with tobramycin alone, colistimethate sodium alone statistically significantly reduced the risk of developing resistance to any inhaled antibiotic ($p<0.05$) or to colistimethate sodium ($p<0.01$). No resistance to colistimethate sodium was recorded among bacterial isolates obtained in Steinfort and Steinfort (2007) or White et al. (2012).

Evidence review: economic issues

Cost

According to MIMS (November 2013), the costs of preparations of colistimethate sodium for inhalation (excluding VAT) are as follows:

- Colobreathe costs £968.80 for 56 capsules containing 1.6625 million units and a Turbospin inhaler.
- Colomycin injection costs £18.00 for 10 vials containing 1 million units of colistimethate sodium and £32.00 for 10 vials containing 2 million units of colistimethate sodium.
- Promixin costs £138.00 for 30 vials containing 1 million units of colistimethate sodium. The price includes the cost of the nebuliser, training, support service and all related consumables.

The costs of these preparations are difficult to compare directly. Colomycin injection and Promixin

are administered using a nebuliser, whereas Colobreathe is administered using a dry powder inhaler. In the case series summarised here, colistimethate sodium was nebulised. The price of Promixin includes the cost of the nebuliser, training, support service and all related consumables, whereas that for Colomycin injection does not. Also, the optimal dose of colistimethate sodium for non-cystic fibrosis bronchiectasis is unclear. Colistimethate sodium was given at a dose of 2 million units twice daily in White et al. (2012), 1–2 million units twice daily in Dhar et al. (2010) and Berlana et al. (2011), and 30 mg daily (estimated to be around 375,000 units) in Steinfort and Steinfort (2007). It is often unclear which preparations were used.

Current drug usage

The Prescription Cost Analysis for England shows that in 2012 11,700 prescription items were dispensed for Promixin (1 million units) at a net ingredient cost of £3,159,400. For Colomycin injection, 23,100 prescription items were dispensed for the vials containing 1 million units, at a net ingredient cost of £2,461,800; 13,200 items were dispensed for the vials containing 2 million units at a cost of £2,427,300. Colomycin injection can be given by intravenous infusion, as well as nebulisation. No information is provided on the proportion used via each route

It is not known what indications these preparations were prescribed for.

Evidence strengths and limitations

No published randomised controlled trials (RCTs) have investigated the use of nebulised or inhaled colistimethate sodium for non-cystic fibrosis bronchiectasis.

Four case series were identified that reported the use of nebulised colistimethate sodium in people with non-cystic fibrosis bronchiectasis and bronchial colonisation with *Pseudomonas aeruginosa*. Case series do not have randomised control groups and are subject to bias and confounding.

White et al. (2012) (n=30), Dhar et al. (2010) (n=19) and Steinfort and Steinfort (2007) (n=18) reported outcomes with nebulised colistimethate sodium, which included exacerbations, hospital admissions, and lung function before and after treatment. Berlana et al. (2011) included 81 people treated with nebulised colistimethate sodium alone, colistimethate sodium plus tobramycin, or tobramycin alone (according to clinical judgement); and primarily compared post-treatment outcomes between the 3 groups, rather than comparing outcomes before and after treatment with nebulised colistimethate sodium.

The case series provide only limited evidence for the effectiveness and safety of inhaled

colistimethate sodium in people with non-cystic fibrosis bronchiectasis. All the case series were small, which may mean they have insufficient statistical power to detect differences in outcomes. Also, all reported on treatment in a single medical centre only, which may lead to selection bias and limits the generalisability to a wider population. Two of the case series were retrospective (White et al. 2012 and Dhar et al. 2010) and therefore dependent on the accuracy of the recorded data.

The case series by White et al. (2012) and Dhar et al. (2010) included only people with non-cystic fibrosis bronchiectasis. However, those by Steinfort and Steinfort (2007) and Berlana et al. (2011) also included small numbers of people with chronic obstructive pulmonary disease and chronic bronchial sepsis, which may affect the applicability of the results.

A range of doses was used in the case series; therefore the optimal dose of colistimethate sodium for non-cystic fibrosis bronchiectasis is unclear. All the case series reported using nebulised colistimethate sodium at dose of 1 or 2 million units twice daily except Steinfort and Steinfort (2007), which reported a dose of 30 mg daily (estimated to be around 375,000 units). The duration of treatment with nebulised colistimethate sodium varied in the individual case series, although it was given long term. In the *Pseudomonas* eradication protocol reported by White et al. (2012), colistimethate sodium was given for 3 months; Berlana et al. (2011) reported use for at least 3 months; and both Dhar et al. (2010) and Steinfort and Steinfort (2007) reported use for at least 6 months.

From the case series, it is not possible to conclude that observed post-treatment effects were due to colistimethate sodium alone. For example, the *Pseudomonas* eradication protocol reported by White et al. (2012) included treatment with other intravenous and oral antibiotics and antibiotics other than those set out in the protocol were used in 8 out of 30 people, mainly because of drug allergy or intolerance. Dhar et al. (2010) excluded from their study people who had used prophylactic macrolide treatment for more than 4 weeks, but no other antibiotic use is discussed. Steinfort and Steinfort (2007) did not report whether there was any other antibiotic use. None of these 3 case series discussed the use of other respiratory drugs. Berlana et al. (2011) reported that people taking colistimethate sodium, tobramycin or both took various respiratory drugs (for example, bronchodilators and corticosteroids) and supplemental oxygen, as well as other antibiotics.

All of the case series used nebulised colistimethate sodium. No studies were identified that investigated the use of the colistimethate sodium dry powder inhaler (Colobreathe, Turbospin) in people with non-cystic fibrosis bronchiectasis.

An RCT, Inhaled Promixin in the treatment of non-cystic fibrosis bronchiectasis, has been

completed but not yet published. Once fully published and peer-reviewed, this study and other RCTs investigating nebulised or inhaled colistimethate sodium for treating non-cystic fibrosis bronchiectasis may give a better indication of the safety and efficacy for this indication.

Summary for patients

A summary written for patients is available on the NICE website.

References

Berlana D, Llop JM, Manresa F et al. (2011) Outpatient treatment of Pseudomonas aeruginosa bronchial colonization with long-term inhaled colistin, tobramycin, or both in adults without cystic fibrosis. Pharmacotherapy 31: 146–57

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

Dhar R, Anwar GA, Bourke SC et al. (2010) Efficacy of nebulised colomycin in patients with non-cystic fibrosis bronchiectasis colonised with Pseudomonas aeruginosa. Thorax 65: 553

Forest Laboratories UK (2012) Colomycin injection summary of product characteristics. [online; accessed 13 November 2013]

Forest Laboratories UK (2013) Colobreathe summary of product characteristics. [online; accessed 13 November 2013]

Haymarket Medical Media (2013) MIMS. [online; accessed 13 November 2013]

Health and Social Care Information Centre (2013) Prescription cost analysis for England 2012. [online; accessed 13 November 2013]

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

ISRCTN Register (2011) Inhaled Promixin® in the treatment of non-cystic fibrosis bronchiectasis. [online; accessed 13 November 2013]

Profile Pharma (2011) Promixin 1 million International Units (IU) powder for nebuliser solution summary of product characteristics. [online; accessed 13 November 2013]

Steinfort DP, Steinfort C (2007) Effect of long-term nebulized colistin on lung function and quality of life in patients with chronic bronchial sepsis. Internal Medicine Journal 37: 495–8

White L, Mirrani G, Grover M et al. (2012) Outcomes of pseudomonas eradication therapy in patients with non-cystic fibrosis bronchiectasis. Respiratory Medicine 106: 356–60

Development of this evidence summary

This evidence summary was developed for NICE by Bazian Ltd. The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.

Appendix: Search strategy and evidence selection

Search strategy

General background, guidelines and technology assessments:

- Broad internet search: Google e.g.: allintitle: bronchiectasis Colistimethate OR Colomycin OR colistin OR coly OR promixin
- Trip Database

MEDLINE (via Ovid)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1. exp Bronchiectasis/ (7478)

2. "bronchiectasi*".af. (9482)

3. 1 or 2 (10301)

4. Colistin/ (2313)

5. (Colistimethate or Colomycin or colistin or coly* or promixin).af. (4179)

6. 4 or 5 (4179)

7. 3 and 6 (18)

Embase (via Ovid)

Database: Embase <1988 to 2013 September 17>

Search Strategy:

1. exp bronchiectasis/ (8343)

2. "bronchiectasi*".af. (9447)

3. 1 or 2 (9849)

4. colistimethate/ (489)

5. (Colistimethate or Colomycin or colistin or coly* or promixin).af. (7410)

6. 4 or 5 (7410)

7. 3 and 6 (141)

8. limit 7 to english language (127)

Cochrane Central Register of Controlled Trials (CENTRAL)

1. MeSH descriptor: [Bronchiectasis] explode all trees

2. bronchiectasis:ti,ab,kw (Word variations have been searched)

3. #1 or #2

4. (Colistimethate or Colomycin or colistin or coly* or promixin):ti,ab,kw (Word variations have been searched)

5. #3 and #4

CRD HTA, DARE and EED database

(Colistimethate or Colomycin or colistin or coly or promixin) and bronchiectasis

Grey literature and ongoing trials

- NHS Evidence
- Health Canada – Clinical Trials Search
- metaRegister of Controlled Trials (mRCT)
- ClinicalTrials.gov

Manufacturers' websites

Forest Labs

Evidence selection

No published randomised controlled trials of colistimethate sodium for non-cystic fibrosis bronchiectasis were identified. After excluding conference abstracts and poster presentations, only 4 observational case series were identified that reported use of nebulised or inhaled colistimethate sodium in this population, and all were included in the evidence summary.

About 'Evidence summaries: unlicensed or off-label medicines'

NICE evidence summaries for off-label or unlicensed medicines summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. They support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

> This document provides a summary of the published evidence. The strengths and weaknesses of the identified evidence are critically reviewed within this summary, but this summary is not NICE guidance and does not provide formal practice recommendations.

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