September 2015

New Medicine Assessment

Colistimethate sodium/Colistin sulfomethate sodium (Colomycin®)

Non-Cystic Fibrosis in Patients with Bronchiectasis Colonised with Pseudomonas Aeruginosa

Recommendation: AMBER 0

Colistimethate sodium (Colomycin®) is recommended as an option for patients with non-cystic fibrosis bronchiectasis, colonised with *Pseudomonas aeruginosa* who have three or more exacerbations per year requiring antibiotics or fewer exacerbations that are causing significant morbidity, in whom long term nebulised antibiotic therapy is being considered.

It is suitable for prescribing in primary care following recommendation or initiation by a specialist.

Summary of supporting evidence:

- The BTS guidelines for bronchiectasis in non-cystic fibrosis patients recommend nebulised antibiotics for patients who have three or more exacerbations per year requiring antibiotics, or fewer exacerbations that are causing significant morbidity.
- These guidelines also recommend that patients with *P.aeruginosa* should have regular follow up in secondary care if they are receiving prophylactic oral or nebulised antibiotic therapy.
- A systematic review (n=1264) evaluating the efficacy and safety of inhaled antibiotics in patients with stable non-CF bronchiectasis concluded that inhaled antibiotics reduce sputum load, eradication of bacteria from sputum and reduce the risk of acute exacerbation compared to placebo or symptomatic treatment. However, the paper found there was no significant benefit in reducing unscheduled hospitalisations or improving health related quality of life.
- Of the twelve trials included in the systematic review, two assessed the use of inhaled colistimethate; one of which was a RCT comparing colomycin to placebo, the other an unpublished open label trial which has not been discussed further in this assessment.
- The RCT (n=144) did not meet the primary endpoint of time to exacerbation. A total of 36 out of 73 (49%) vs. 42 out of 71 (59%) experienced an exacerbation during the 6 months for colomycin and placebo respectively. Median time (25% quartile) to exacerbation was 165 days (42 days) in the colistin group vs. 111 days (52 days) for placebo (p=0.11).
- A subgroup analysis of those patients who complied with therapy (≥ 81%) demonstrated a significant reduction in exacerbations compared to placebo; 27 out of 54 (50%) vs. 37 out of 52 (71%) (p=0.038) respectively. However, the study was not powered to show this and therefore we cannot reliably conclude whether this was as a result of treatment difference or chance.
- Quality of life measured using the SGRQ showed an estimated mean treatment difference in change in total SGRQ score for inhaled colistin of -10.51 (95% CI, -17.87 to -3.14) (p=0.006) at week 26. A reduction of 4 units or more is considered clinically significant.

Produced September 2015
Midlands and Lancashire CSU, 2015

- The mean treatment difference in weight of sputum from baseline to week 4 was not statistically significant.
- Three retrospective and one prospective observational study in patients with non-cystic fibrosis bronchiectasis and *P. aeruginosa* colonisation (n=148) evaluated the effect of nebulised colistimethate sodium. However, one of the studies used a different dosing schedule to that which is recommended and the individual studies had small numbers of patients.
- Two of case series found no significant effect on hospital admissions, the other found a reduction in the mean number of hospital admissions before and after treatment from 3.0 to 0.95 per year (p=0.002). Two of the case series found a statistically significant reduction in the number of exacerbations needing antibiotics compared to before treatment.
- One study found a statistically significant reduction in the number of positive *pseudomonas* samples from 4.2 per year to 0.5 per year, the other found initial eradication of *pseudomonas* but after a median of 6 months nearly 50% experienced a recurrence. All three case series found no significant effect on FEV_1.
- The prospective case series found no significant differences in the mean number of hospital admissions (1.6 admissions compared with 1.9 per person per year), duration of hospital stay (19.7 days compared with 22.5 days per person per year), or duration of antibiotic use (15.4 days per person per year compared with 14.8 days per person per year) between colistimethate sodium and tobramycin.

- The systematic review found the only statistically significant difference in reported AEs compared to control group was for bronchospasm, which occurred in 10% of patients. However, it was found that for the colomycin subgroup this difference was not statistically significantly different compared to placebo; five (7%) patients in the colistin group of the RCT developed bronchoconstriction that led to treatment discontinuation.
- No colistimethate-resistant strains of *P. aeruginosa* were identified during the study and there were no significant differences in treatment-emergent pathogens between treatment groups.
- 143 AEs were reported in the RCT in 47 patients (64%) in the colistin group vs. 108 AEs in 38 patients (54%) for the placebo group (p=0.25). The incidence of adverse events leading to discontinuation of the study drug was low; 9.6% and 8.5% patients in colistin group and placebo group, respectively.
- The NRLS identified incidents of errors with colistimethate sodium preparations. Of particular concern were incidents when the wrong strength was prescribed, dispensed or administered.
- The UKMI assessment found that there are some risks with prescribing, product selection and administration of colistimethate sodium products.

- Colomycin 1 million unit vials twice daily, cost £1314 annually; colomycin 2 million unit vials twice daily, cost £2365 annually. In addition, Saline Steripoules required for dilution currently cost £493 annually.
- Current spend across Lancashire for the financial year 2014/15 for generic colistimethate sodium 1 million and 2 million unit vials together with the branded Colomycin 1 million and 2 million unit vials was £139,480.45, however all this prescribing will not be attributed to the prophylaxis in non-CF bronchiectasis.

Produced September 2015

Details of Review

Name of medicine (generic & brand name)**:**

Colistimethate sodium (Colomycin®)

N.B. A cheaper, generic version is also listed in the BNF. However the SPC does not list for use via nebulisation as a licensed indication for the generic version and it may not be easily obtainable. In addition, Promixin powder for nebuliser solution is available but at a greater cost.

Strength(s) and form(s):

1 million unit and 2 million unit vials for nebulisation

Dose and administration:

1 million units twice daily by nebulisation or 2 million units twice daily by nebulisation (for proposed indication)

BNF therapeutic class / mode of action

5.1.7 Some other antibacterials > Polymixins

Licensed indication(s):

Colomycin is indicated in the treatment of the following infections where sensitivity testing suggests that they are caused by susceptible bacteria:

- Treatment by inhalation, of *Pseudomonas aeruginosa* (*P. aeruginosa*) lung infection in patients with cystic fibrosis (CF).
- Intravenous administration for the treatment of some serious infections caused by Gram-negative bacteria, including those of the lower respiratory tract and urinary tract, when more commonly used systemic antibacterial agents may be contra-indicated or may be ineffective because of bacterial resistance.

Proposed use (if different from, or in addition to, licensed indication above):

Prophylaxis against recurrent *P. aeruginosa* infection in non-cystic fibrosis patients (unlicensed indication)

Course and cost (MIMS May 2015): (powder in vials):

Colomycin 1 million units twice daily dosing £1,314 for 1 year's supply

Colomycin 2 million units twice daily dosing £2,365 for 1 year's supply

Saline Steripoules 20 x 2.5 mL vials twice daily for dilution £493 for 1 year's supply

Please note colistimethate sodium is listed as a high cost drug (PbRe) when delivered by nebulisation/inhalation.

Produced September 2015
Midlands and Lancashire CSU, 2015

Current standard of care/comparator therapies:

Tobramycin 300 mg by nebulisation every 12 hours for 28 days. Subsequent courses repeated after a 28 day interval without tobramycin nebuliser powder.

Gentamicin 80 mg by nebulisation twice daily.

Relevant NICE guidance:

NICE Evidence Summary: ESUOM25: Non-cystic fibrosis bronchiectasis: colistimethate sodium 6/1/14

Background and context

Clinical bronchiectasis can be defined as persistent or progressive sepsis related to irreversibly damaged and dilated bronchi.[1] The symptoms vary from intermittent episodes of expectoration and infection localised to the region of the lung that is affected, to persistent daily expectoration often of large volumes of purulent sputum. The incidence of bronchiectasis varies widely between different populations across the world. In the UK there are no recent studies. The prevalence increases with age. Mass chest x-ray features of bronchiectasis in 1950s suggested a prevalence of 100 per 100,000.

Bronchiectasis is caused by chronic inflammation of the airways and is associated with a wide range of diseases. Focal bronchiectasis may be due to bronchial obstruction, such as by a foreign body, tumour, or compression by peri-bronchial lymph nodes or prior severe respiratory infection. Diffuse bronchiectasis is thought to have a range of causes including: infection, such as whooping cough, measles, or pneumonia; rheumatoid arthritis; allergic bronchopulmonary aspergillosis (ABPA); immunodeficiency, such as common variable immunodeficiency (hypogammaglobulinaemia) or HIV infection; cystic fibrosis; primary ciliary dyskinesia; inflammatory bowel disease; aspiration, for example from gastro-oesophageal reflux; yellow nail syndrome; and other congenital disorders, such as: alpha-1 antitrypsin deficiency; Young's syndrome (characterized by bronchiectasis, rhinosinusitis, and reduced fertility caused by abnormally viscous mucus); and Marfan's syndrome (a genetic disorder of connective tissue). However in some patients, no cause or association may be identified.[2]

The healthy lung is sterile due to a sophisticated defence mechanism. Mucociliary clearance is impaired in bronchiectasis which facilitates bacterial growth and colonisation on the surface of the airways. The subsequent neutrophil inflammation causes airway damage, further impairing host defences setting up a self-perpetuating cycle of events.[1]

P. aeruginosa is a persistent pathogen in patients with bronchiectasis due to its ability to produce virulence factors and modulate immune defences by biofilm production. Patients chronically colonised with *P. aeruginosa* have increased hospital admissions, worse quality of life and may have an accelerated decline in FEV_1.[1] The British Thoracic Society guidelines for bronchiectasis in non-cystic fibrosis patients, published in July 2010, recommend the prescription of nebulised

Produced September 2015

antibiotics in such patients if they have had three or more exacerbations per year requiring antibiotics, or fewer exacerbations that are causing significant morbidity.

The aims of treatment for non-cystic fibrosis bronchiectasis are to maintain and improve lung function by identifying and treating any underlying causes; to reduce exacerbations, control symptoms, and improve quality of life. Treatments may include airway clearance using physiotherapy, pulmonary rehabilitation, antibiotics, bronchodilators, and surgery. It is thought that by prescribing long-term antibiotics, this may reduce bacterial load in the airways, limit inflammation and reduce the volume and purulence of sputum. The BTS guidelines recommend that antibiotics should be given for exacerbations that present with acute deterioration and worsening symptoms and/or systemic illness. Sputum culture should guide antibiotic therapy and that empirical antibiotics should be given until the results are known. Ciprofloxacin should be prescribed first line for those with confirmed *P. aeruginosa.* The BTS guidance recommends that patients with chronic *P. aeruginosa* should have regular follow up in secondary care if they are receiving prophylactic oral or nebulised antibiotic therapy. No approved inhaled antibiotic is indicated for the treatment of non-cystic fibrosis bronchiectasis.[3]

Colistimethate sodium (Colomycin®, Colobreathe® and Promixin®) is a polymixin antibiotic with activity against gram negative bacteria. It is licensed for treating chronic pulmonary infections caused by *P. aeruginosa* in cystic fibrosis but not in non-cystic fibrosis bronchiectasis. Use of nebulised colistimethate sodium for non-cystic fibrosis is therefore off-label.[4] Colistimethate sodium is poorly absorbed from the gastrointestinal tract and is not absorbed through mucous membranes, or intact or denuded skin. Transpulmonary absorption is variable following inhalation of nebulised solution of a dry powder.[5]

Other treatment options include nebulised tobramycin and nebulised gentamicin. Colomycin therapy is significantly cheaper than tobramycin therapy[6] and is a safer alternative to gentamicin. Only some brands of gentamicin may be used for nebulisation due to the risk of bronchoconstriction caused by certain excipients. In addition colomycin has fewer risks associated with its preparation than gentamicin as gentamicin preparation involves breaking a glass ampoule and the safe use of a filter needle to draw up the contents.[7] The BTS guidelines state that choice of antibiotic should be guided by the antibiotic sensitivity results and that further studies are needed to address the optimal antibiotic choice and doses required.[1]

In January 2014, NICE issued an evidence summary entitled ESUOM25: Non-cystic fibrosis bronchiectasis: colistimethate sodium.[4] This evidence review summarised four small case series (at the time of publication a randomised controlled trial, which is discussed in "summary of evidence" section below, had not been published) and concluded that these case series provided weak evidence for the safety and effectiveness of nebulised colistimethate sodium for treating non-cystic fibrosis bronchiectasis and colonisation with *P. aeruginosa*.

Summary of evidence

Summary of efficacy data in proposed use:

A systematic review to evaluate the efficacy and safety of inhaled antibiotics in patients with stable non-CF bronchiectasis & chronic bronchial infection, published in 2014, was identified.[8] Twelve trials with 1264 adults, 656 allocated to inhaled antibiotics, were included, of which five trials were unpublished. The meta-analysis consisted of eight trials (n=590). The included drugs were amikacin, aztreonam, ciprofloxacin, gentamicin, colistin or tobramycin which were used for between 4 weeks and one year. Only two of the twelve trials included in the systematic review, assessed the use of inhaled colistimethate; one of which was a RCT comparing colomycin to placebo, the other an unpublished open label trial which has not been discussed further in this assessment and was not included in the meta-analysis.[9,10] The reliability of the results of the systematic review are questionable in view of the fact that one of the two Colistin trials included has not been fully published. Inhaled antibiotics were more effective than placebo or symptomatic treatment in reducing sputum bacterial load (five trials; weighted mean difference -2.65 [95% CI -4.38 – -0.92 $\log_{10}$ CFU*g^{-1}] p=0.003); eradicating the bacteria from sputum (six trials; risk ratio 4.2 [95% CI 1.62–10.64] p=0.003 NNT=3) and reducing the risk of acute exacerbations (five trials; risk ratio 0.72 [95% CI 0.55–0.94] p=0.02 NNT=5). The systematic review concluded inhaled antibiotics reduce sputum bacterial load, eradication of bacteria from sputum and reduce risk of acute exacerbation compared to placebo or symptomatic treatment in adult patients with stable non-CF bronchiectasis and chronic bronchial infection. The review did not find a significant benefit in reducing unscheduled hospitalisations or improving health related quality of life.

The results of the phase III randomised, double-blind, multi-centre, placebo-controlled trial included in the systematic review are included in the table (Appendix 1).[9] It compared the use of nebulised colistin 1 million international units in 1mL 0.45% saline with placebo of 1mL 0.45% saline, nebulised twice daily for 6 months, in 144 adults with bronchiectasis and chronic *P. aeruginosa* (two or more positive respiratory tract cultures in the preceding 12 months), enrolled within 21 days of completing a course of antipseudomonal antibiotics for the treatment of an exacerbation. The study was designed in this way in order to provide a uniform starting point for the primary endpoint of time to first exacerbation. Patients prescribed other inhaled antibiotics were eligible for the study if they discontinued treatment at the screening visit.

Of the 73 patients assigned to colistin, 11 withdrew early. Therefore 62 patients in the active comparator arm completed the study. Of the 71 patients randomly assigned to placebo, 11 also withdrew early: 4 had an AE, 2 withdrew due to ineffective therapy, 4 withdrew consent and 1 was withdrawn from the study after receiving the first dose of investigation medicinal product because she did not meet the entry criteria (>15% fall in FEV_1 within 30 minutes of the first dose).

The study failed to meet the primary endpoint of time to exacerbation. A total of 36 out of 73 (49%) patients in the colistin group experienced an exacerbation in comparison to 42 out of 71 (59%) in the placebo group. The median time (25% quartile) to exacerbation was 165 days (42 days) in the colistin group and 111 days (52 days) in the placebo group (p=0.11). Figures reported by the investigators in the text of the article but not within the tables, state that there was a greater number of exacerbations within the poorly adherent patients (not defined), assigned colistin 8 of 16 (50%) compared with 5 of 18 (28%) in the placebo group. This could be a possible explanation for the study failing to meet the primary endpoint.

The secondary efficacy endpoints (see Table 1) included time to first exacerbation based on adherence. This was measurable by means of the I-Neb adaptive aerosol delivery device which provided a precise record of nebuliser use through an electronic download. To examine the effects of adherence on efficacy, the time to exacerbation was summarised in quartiles based on percentage adherence. When patients in adherence quartile one were excluded from the analysis (adherence <81% i.e. patients who were concordant with the dosage instructions less than 81% of the study period, as measured by the I-Neb), thus combining data from adherence quartiles 2-4; 27 of 54 (50%) patients in the colistin group had an exacerbation compared with 37 of 52 (71%) in the placebo group (p=0.038). This represented a treatment difference of 65 days in time to exacerbation between the colistin and placebo groups.

The St. George's Respiratory Questionnaire (SGRQ), a secondary efficacy endpoint, was used as a way of measuring the impact of nebulised colomycin on overall health, daily life, and perceived well-being in the cohort. The mean (SD) change in SGRQ total score from baseline for colomycin to week 12 and week 26 was -2.8 (14.5) and -10.4 (19.6) units, respectively, compared to -2.2 (10.5) and -0.4 (13.2) units for the placebo group. The treatment difference reached statistical significance at Week 26 (P = 0.006). A reduction in score of 4 units is considered clinically significant,[11] thus the 10.4 unit reduction seen with nebulised colistin at week 26, would imply this intervention produced clinically significant results. Inhaled colistin resulted in significant reductions in *P. aeruginosa* density after 4 and 12 weeks treatment, compared with placebo (see Table 1).

The estimated mean treatment difference in weight of sputum from baseline to week 4 was not statistically significant at -1.9 g (95% CI, -8.3 to 4.5; p=0.56). With regards to severity of exacerbations, most exacerbations (75% and 79% in the colistin and placebo groups, respectively) were treated with oral antibiotics, classified as a moderate exacerbation.

Other efficacy data:

Three retrospective[12,13,14] and one prospective[15] case series were identified with a total population of 148 patients with non-cystic fibrosis bronchiectasis and *P. aeruginosa* bronchial colonisation. These patients received nebulised colistimethate sodium in the following dosing schedules; 2 million units twice daily for 3 months[12], 1-2 million units twice daily for a mean of 21.2 months (range 6-39 months)[13], 30 mg daily over 6-116 months[14] and either 1 million units or 2 million units twice daily every 12 hours, alone or in combination with tobramycin over a mean duration of treatment of 633.7 days (+/- 480.3) for colistimethate sodium alone and 657.6 days (+/-561.1) in combination with tobramycin.[15]

Produced September 2015
Midlands and Lancashire CSU, 2015

The three retrospective case series[12,13,14] compared outcomes using historical self-controls before and after treatment with nebulised colistimethate sodium in 30, 19 and 18 patients respectively. Two of these case series[12,13] found that treatment statistically significantly reduced the mean number of exacerbations needing antibiotics from 3.93 before treatment to 2.09 per year after treatment ($p<0.002$) for one study and the mean number for exacerbation from 7.8 to 2.7 per year before and after treatment respectively($p<0.001$) for the second study. The third case series did not report rate of exacerbations.

Two case series[12,14] found that treatment had no significant effect on hospital admissions, one[13] found that treatment statistically significantly reduced the mean number of hospital admissions before and after treatment (from 3.0 to 0.95 per year, $p=0.002$). All three retrospective case series[12,13,14] found that treatment had no significant effect on FEV_1. However, one of the three case series[14] found that treatment 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 ($p=0.033$)). Two case series[12,13] measured mean number of *Pseudomonas* positive samples. One[12] found that *Pseudomonas* was initially eradicated from the sputum of 24/30 (80%) patients, 13 (54%) remaining *Pseudomonas*-free at their latest follow-up (median 14.3 months). 11 (46%) of these patients experienced a recurrence of *Pseudomonas* (median time to re-infection 6.2 months). The other study[13] found that colistimethate sodium statistically significantly reduced the mean number of positive samples for *Pseudomonas* from 4.2 per year to 0.5 per year ($p<0.001$).

The prospective case series[15] was an observational study in patients with non-CF bronchiectasis (n=83) or COPD (n=14) who had received long-term (at least 12 weeks) nebulised treatment for *P. areuginosa* bronchial colonisation between January 2004 and December 2008. The study compared nebulised courses of colistimethate sodium alone (1 to 2 million units twice daily) (n=31), nebulised tobramycin alone (n=50) or both (n=16) (not discussed), in 81 patients outpatients. There were no significant differences in the mean number of hospital admissions (1.6 admissions compared with 1.9 per person per year), duration of hospital stay (19.7 days compared with 22.5 days per person per year), or duration of antibiotic use (15.4 days per person per year compared with 14.8 days per person per year) between the colistimethate sodium and tobramycin groups respectively. The paper did not provide P values.

Summary of safety data:

Systematic Review data:

The systematic review found there was a only statistically significant difference in reported AEs compared to control group for bronchospasm, which occurred in 10% of patients treated with inhaled antibiotics and 2.3% in the control group (seven trials n=526; risk ratio 2.96, 95% CI 1.30-6.73; p=0.01). However the subgroup analysis for inhaled colistin showed it was not significantly associated with bronchospasm (one trial n=144; risk ratio 4.86, 95% CI 0.58-40.59, p=0.14). There were no statistically significant differences between inhaled antibiotic and control group in terms of withdrawal rate due to AEs and other respiratory complaints such as cough and haemoptysis. Seven trials reported the rate of emergence of bacterial resistance (number of isolates classified as resistant to the antibiotics/total number of isolates from sputum samples) in

the inhaled antibiotic and control groups, but different methods were used for antibiotic susceptibility testing. The meta-analysis of seven trials with a total 445 patients did not show a statistically significant difference in the incidence of emergence of bacterial resistance between the inhaled antibiotic use (17/217 (7.8%) vs. 8/228 (3.5%) Risk ratio 1.68 95% CI 0.62-4.52 (p=0.31)).[8.II]

RCT data:

Secondary safety endpoints measured in the RCT were; bronchoconstriction in the 30 minutes post-first dose of the study drug, FEV_1, sensitivity of Ps aeruginosa to colistin; Colony Forming Units (CFUs) of other potentially pathogenic micro-organisms and adverse event (AE) reporting. One patient in the placebo group experienced a reduction in FEV_1 of greater than or equal to 15% within 30 minutes of the first dose and discontinued treatment. Five (7%) patients in the colistin group subsequently developed bronchoconstriction that led to treatment discontinuation. The estimated mean treatment difference in FEV_1 (L) from baseline to weeks 4, 12 and 26 did not reach statistical difference for the inhaled colistin group compared to placebo (see Table 1). No colistin-resistant strains of *P. aeruginosa* were identified during the study. There were no significant differences in treatment-emergent pathogens between treatment groups.[9]

A total of 143 AEs were reported in 47 patients (64%) in the colistin group and 108 AEs in 38 patients (54%) in the placebo group (p=0.25). There were three deaths, which were all considered unlikely related to the study drug by the investigator. One death, defined as cardiopulmonary failure, occurred in the colistin group. Two deaths, defined as bronchiectasis and respiratory failure in one patient and acute coronary syndrome in the remaining patient, occurred in the placebo group. The incidence of adverse events leading to discontinuation of the study drug was low (9.6% and 8.5% patients in colistin group and placebo group, respectively). The authors state that there were no safety concerns related to the use of nebulised colistin and no concerns with respect to renal toxicity or neuropathy, specifically. However, a description of the types of AEs reported in this study is not documented in the paper.[9]

Case series data:

Two studies[12,13] did not report adverse events, and one study[14] reported that there were no adverse events with colistimethate sodium, one patient stopped treatment because of perceived inefficacy. In one study, 3 out of 30 patients (10%) did not receive nebulised colistimethate sodium because of intolerance.[12] In another study, two patients stopped treatment – one did this in error and one stopped due to lack of efficacy.[13] In the final study[15], drug-related adverse events were reported by 58% of people (29/50) who took colistimethate sodium alone, most commonly dyspnoea (21% 6/50 patients), bronchospasm and cough (each affecting 12% 6/50 of patients), wheezing (10%, 5/50) and dry mouth (6% 3/50). There was no significant difference between the colistimethate sodium treated group and those managed with tobramycin in terms of drug-related AEs; (58% (29/50 patients) with colistimethate sodium alone vs. 28% (20/72 patients) with tobramycin alone (p=0.24)) or withdrawals because of AEs (26% (13/50 patients) with colistimethate sodium, 13% (9/72 patients) with tobramycin (p=0.06)).

The summary of product characteristics for Colomycin[16] states that inhalation may induce

coughing or bronchospasm. Sore throat or mouth has been reported and may be due to *Candida albicans* infection or hypersensitivity. Skin rash may also indicate hypersensitivity, if this occurs treatment should be withdrawn.

Strengths and limitations of the evidence:

Strengths

- The validity for the RCT is likely to be high and the risk of bias low due to the following reasons: Patient-oriented outcomes, allocation concealment, double blinding, intention-to-treat analysis, adequate power and size as well as adequate follow-up.
- Three of the case studies[12,13,14] reported patient oriented outcomes with nebulised colistimethate sodium, including exacerbations, hospital admissions and lung function, before and after treatment.
- One study[15] was an active comparator trial, comparing outcomes between three different groups of patients (nebulised colistimethate sodium alone, nebulised tobramycin alone or colistimethate sodium plus tobramycin). However the patient population was small and included COPD patients in addition to patients with non-CF bronchiectasis.

Limitations

- The systematic review included only two trials involving patients prescribed inhaled colistimethate sodium, one of which is not fully published and is only available as a conference abstract. Therefore the reliability of the conclusions is questionable.[8]
- The RCT did not meet the primary outcome therefore a subgroup analysis was carried out, which demonstrated that those patients who complied with therapy showed significant reduction in exacerbations compared to placebo. However, this subgroup was not powered to show statistical significance so we cannot reliably conclude the difference was as a result of the treatment or due to chance.[9]
- Specific descriptions of the AEs reported by the participants in the RCT were not included in the paper.
- Similarly, the percentage of severe exacerbations in each group in the RCT is not stated but implied by means of reporting the percentage of moderate exacerbations only.
- As the case studies do not have randomised controlled groups, they are subject to bias and confounding factors.
- All the case studies were small and so were insufficiently powered to detect differences in outcomes. All patients were treated in a single treatment centre only which may lead to selection bias and limits generalisability to a wider population.
- The retrospective case series results were dependent on the accuracy of the data which was recorded.
- Two studies[14,15] included small numbers of patients with conditions other than non-cystic fibrosis bronchiectasis which may affect the applicability of the results.
- One study[14] used a dose of 30 mg daily of colistimethate sodium (estimated to be approximately 375 000 units daily).

- It is not possible to conclude from any of the four case studies that the post-treatment effects which were observed were as a result of colistimethate sodium alone. This is either due to non-reporting of other antibiotic use or because other intravenous and/or oral antibiotics and/or other respiratory drugs, were used in the studies.

Summary of evidence on cost effectiveness:

Health Technology Assessment bodies in the UK have not yet assessed the cost-effectiveness of colistimethate sodium in non-cystic fibrosis bronchiectasis patients colonised with *P. aeruginosa*.

Prescribing and risk management issues:

- The British Thoracic Society advised that when nebulised antibiotic treatment is used, a multi-disciplinary team that includes a chest physician, physiotherapist and respiratory nurse should co-ordinate care. The patient should receive ongoing support once treatment is initiated. Compressors and nebulisers that meet British and European performance and safety standards should be used.[1]
- Patients need to be taught how to use the colistimethate sodium vials and administer the correct dose via the nebuliser. SPC advises use of the nebuliser should occur in a well-ventilated room.
- Potential AEs should be discussed with the patient.
- Prescribing by specialists only can lead to risk management issues such as primary care clinicians and community pharmacists being unaware the patient is being prescribed colomycin if their patient medication records are not updated fully. In addition, ordering of colistimethate sodium may not be synchronised with other medication and patients may need to attend a hospital setting to collect this medication, depending on traffic light status.
- Choice of antibiotic should be guided by sensitivity results, as per BTS guidelines. Long term antibiotics use may result in resistance and alternatives dependent on sensitivity results should be chosen.
- Results from the RCT indicate adherence to twice daily nebulisation of colistimethate sodium can be an issue for patients and may result in reduced efficacy of the drug. Importance of adherence to the drug regime must be emphasised to patients.

SPC states:

- Mixed infusions, injections and nebuliser solutions involving colistimethate sodium should be avoided. For local treatment of lower respiratory tract infections Colomycin powder is dissolved in 2-4 ml of water for injections or 0.9% sodium chloride intravenous infusion for

Produced September 2015

use in a nebuliser attached to an air/oxygen supply.

- Concomitant use of inhaled colistimethate sodium with other medicines that are nephrotoxic or neurotoxic should only be undertaken with the greatest caution. These include the aminoglycoside antibiotics such as gentamicin, amikacin and tobramycin. There may be an increased risk of nephrotoxicity if given concomitantly with cephalosporin antibiotics.
- Neuromuscular blocking drugs and ether should be used with extreme caution in patients receiving colistimethate sodium.
- Bronchospasm may occur on inhalation of antibiotics. This may be prevented or treated with appropriate use of beta$_2$-agonists. If troublesome, treatment should be withdrawn.
- Use with caution in renal impairment. It is advisable to assess baseline renal function and to monitor during treatment.
- Colistimethate sodium is contra-indicated in myasthenia gravis and hypersensitivity to colistimethate or polymixin B and should be used with extreme caution in patients with porphyria.

BNF states:

- Other inhaled drugs should be administered before colistimethate sodium.
- Measure lung function before and after initial dose and monitor for bronchospasm; if bronchospasm occurs in a patient not using a bronchodilator, repeat test using a bronchodilator before the dose of colistimethate sodium.
- Risk of further haemorrhage in severe haemoptysis.

UKMi In Use Product Safety Assessment Report for Colistimethate Sodium June 2015[17]

- The National Reporting and Learning System (NRLS) identified incidents of errors with colistimethate sodium preparations. Of particular concern were incidents when the wrong strength was prescribed, dispensed or administered.
- Differences in expression of strength in the EU compared to other regions, such as the USA and Australia, have led to errors in international medical literature.[18]
- The European Medicines Agency (EMA) completed a review in October 2014 from which there were several findings; significant gaps exist in the literature in relation to dosing in special populations (for example in children and in patients with renal impairment). This led to recommendations to ensure consistent expression of doses in International Units (IUs), consistent dosing recommendations across product literature, and inclusion of a product strength conversion table (IUs and milligrams) to address confusion arising from international medical literature.
- The UKMi assessment, using a validated assessment tool, [19] reviewed UK licensed colistimethate sodium products given by nebulised and parental routes and summarised the considerations associated with their in-use safety within the NHS. It found that there are some risks associated with the prescribing, product selection and administration of colistimethate sodium products.
- The product information for Colomycin (Forest Laboratories) and Colistimethate sodium (Beacon Pharmaceuticals) remained to be updated with the product strength conversion table in-line with the EMA recommendations.

- The UKMi assessment also concluded, following the application of the validated assessment tool, that the specifics for preparing nebulised colistimethate sodium for administration, can vary according to which product is selected as well as the type of nebuliser being used. It notes that during administration, certain precautions need to be taken to prevent exposure of the nebulised drug into the environment. One way of doing this is to ensure the room is well-ventilated or may require tubing or filters to prevent waste from entering the environment. The assessment noted there was potential for risk associated with this when home use was anticipated. The safety assessment report recommended that strategies to mitigate any risks of exposure to nebulised colistimethate sodium into the local environment should be included in local protocols to ensure administration is only within this context. In addition there should be good patient counselling to ensure safe administration in the home.
- The UKMI assessment stated that, "products intended for intravenous use but used 'off-label' as a nebuliser solution, is an area of some potential contention; the specific pharmaceutical issues associated with it are beyond the scope of this paper. Regardless, the variations in licensing should be taken into account when selecting an appropriate product at the point of prescribing, dispensing, and administration."[17]

Commissioning considerations:

Comparative unit costs:

Drug	Example regimen	Pack cost	Cost per patient per course/ per year (ex VAT)
Colomycin 1 million unit vials	1 million units twice daily for 12 months	£18.00 for 10 vials	£1314
Colomycin 2 million unit vials	Colomycin 2 million units twice daily for 12 months	£32.40 for 10 vials	£2365
Tobramycin 300 mg/4 mL nebuliser solution (Bramitob®)	Tobramycin 300 mg every twelve hours for 28 days x 6 months	£1187 for 56 x 4 mL vials	£7122
Gentamicin 40 mg/mL injection (Gentacin®)	Gentamicin 80 mg twice daily	£10 for 10 x 2 mL 40 mg/mL amps	£130
Costs based on MIMS list prices 11/5/15 This table does not imply therapeutic equivalence of drugs or doses.			

Associated additional costs or available discounts:

- Saline solution - £493 annually for Saline Steripoules for Colomycin and Gentamicin.

Produced September 2015
Midlands and Lancashire CSU, 2015

Productivity, service delivery, implementation:

- If prescribing were restricted to red traffic light status, patients would need to attend hospital to collect their prescription for colistimethate sodium, which could have an impact on clinic capacity and additional cost of clinic appointment.

Anticipated patient numbers and net budget impact:

- The application form for this New Medicines Assessment was received from Blackpool, Fylde and Wyre Hospitals NHS Trust and anticipated patient numbers for the patients from this trust alone are approximately 100 patients. This equates to £208 780 for 100 patients prescribed Colomycin 1 million units twice daily for one year with Saline Steri-Nebs for dilution.
- The Prescription Cost Analysis for England showed that in the financial year 2014/15 a total of 1311 items were dispensed in Lancashire for generic colistimethate sodium 1 million and 2 million unit vials together with the branded Colomycin 1 million and 2 million unit vials, at a net ingredient cost of £139,480.45. No Promixin prescribing was identified.
- No information is available on the proportion of vials used either intravenously or via nebulisation. Similarly, it is not known what indication these preparations were prescribed for.

Total items 2014/15

CCG	Colistimethate sodium 1 million units injection	Colistimethate sodium 2 million units injection	Colomycin 1 million units injection	Colomycin 2 million units injection	Total
Blackburn with Darwen	23	18	3	2	46
Blackpool	104	0	186	62	352
Chorley and South Ribble	24	0	96	19	139
East Lancashire	20	1	88	18	127
Fylde and Wyre	63	8	127	33	231
Greater Preston	38	1	226	9	274
Lancashire North	16	12	48	29	105
West Lancashire	0	0	27	10	37
Total	288	40	801	182	**1311**

Produced September 2015
Midlands and Lancashire CSU, 2015

Total cost (£) 2014/15

CCG	Colistimethate sodium 1 million units injection	Colistimethate sodium 2 million units injection	Colomycin 1 million units injection	Colomycin 2 million units injection	Total
Blackburn with Darwen	£4524.18	£3232.95	£299.59	£359.19	£8415.91
Blackpool	£11,647.06	0	£15,962.60	£10,970.16	£38,579.82
Chorley and South Ribble	£1563.67	0	£8866.47	£2211.21	£12,641.35
East Lancashire	£2295.36	£179.66	£8362.99	£3521.69	£14,359.70
Fylde and Wyre	£7723.41	£869.17	£12,155.04	£5774.62	£26,522.24
Greater Preston	£3694.32	£179.52	£17,825.17	£1616.55	£23,315.56
Lancashire North	£1397.31	£2155.90	£3460.41	£4522.02	£11,535.64
West Lancashire	0	0	£3211.61	£898.62	£4110.23
Total	£32,845.31	£6617.20	£70,143.88	£29,874.06	**£139,480.45**

Innovation, need, equity:

- Colomycin is the current treatment of choice for non-cystic fibrosis bronchiectasis with pseudomonal colonisation at Blackpool, Fylde and Wyre Teaching hospitals, staff are familiar with using colomycin nebulisers and the patient education required. Wythenshawe hospital, a tertiary respiratory centre in the North West, also advocates the use of colomycin for this indication.
- Colomycin use in this cohort of patients is not considered innovative as it is established practice.
- Patients may have difficulty making regular visits to hospital to collect their prescription if this remains a hospital only red drug. However if BTS guidance is followed, these patients will already have regular outpatient appointments. One hospital trust reports patients being followed up 3-6 monthly.
- The BTS guidelines state that choice of antibiotic should be guided by the antibiotic sensitivity results. Therefore colistimethate sodium needs to be available as an option dependent on sensitivity results.

Produced September 2015
Midlands and Lancashire CSU, 2015

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Produced September 2015

Table: Summary of key inhaled colistimethate sodium RCTs relevant to use in for non-cystic fibrosis bronchiectasis

Ref	Trial design	Patients / Trial subjects	Trial intervention and comparison	Outcomes: Primary endpoint (mITT)	Outcomes: Key secondary / exploratory endpoints	Grading of evidence / risk of bias
Haworth C.S, Foweraker J.E, Wilkinson P et al. Inhaled Colistin in Patients with Bronchiectasis and Chronic Pseudomonas aeruginosa Infection *Am J Respir Crit Care Med* 2014 189;8:975-982.	Phase III Randomised double-blind placebo-controlled study (n=144) conducted at 35 centres in the UK, Ukraine and Russia between March 2009 and February 2012	Adults with bronchiectasis (confirmed by CT) and chronic P. *aeruginosa* (two or more positive respiratory tract cultures in the preceding 12 months) enrolled within 21 days of completing a course of antipseudomonal antibiotics for an exacerbation. P. *aeruginosa* also had to be cultured from a sample taken at the screening visit. **Baseline characteristics** Mean age (yrs): 59.5 Female: 57.6% Mean FEV_1 (L): 1.55 Mean % predicted FEV_1 (SD): 56.8% Mean weight of sputum collected over 24 hours (g) before baseline visit (SD): 28.3 Azithromycin therapy n (%): 11 (7.6%) Prior inhaled antibiotic therapy: 0 **Exclusion criteria:**	Randomly assigned to: colistin 1 million international units in 1 mL 0.45% saline administered twice daily for 6 months (n=73) 1 mL of 0.45% saline administered twice daily for 6 months (n=71)	**Time to exacerbation**: 36/73 (49%) in the colistin group experienced an exacerbation in vs. 42/71 (59%) in the placebo group. Statistical significance not stated. The median time (25% quartile) to exacerbation 165 days (42 days) in the colistin group and 111 days (52 days) in the placebo group (P=0.11).	**Time to exacerbation based on adherence** recorded by the I-neb (summarised in quartiles based on percentage adherence): In the second quartile (adherence 81-92.1% n=34 P=0.017) 6/17 (35%) patients in the colistin group experienced an exacerbation vs. 14/17 (82%) in the placebo group. P value not reported (paper states statistically significant). Within the first quartile (adherence <81%; n=34), third quartile (adherence 92.1-97.1%; n=36) and fourth quartile (adherence >97.1%; n=36 patients) no evidence of treatment group difference. Quartiles 2-4 combined (adherence ≥81%) 27 of 54 (50%) patients in the colistin group had an exacerbation vs. 37 of 52 (71%) in the placebo group. Median time (25% quartile) to exacerbation was 168 days (65 days) in the colistin group and 103 days (37	Patient-oriented outcome measure?: Yes Allocation concealment?: Yes Blinded if possible?: Yes Intention to treat analysis?:Yes Adequate power/size?: Yes Adequate follow-up (>80%)?: Yes Level 2 evidence based on POO. Risk of bias: low based on all of the above.

Produced September 2015
Midlands and Lancashire CSU, 2015

		History of: cystic fibrosis, primary ciliary dyskinesia, hypogammaglobulinaemia, myloproliferative disease, solid organ or bone marrow transplantation, requirement for immunosuppressive medication, HIV infection, inflammatory bowel disease, myasthenia gravis, active allergic bronchopulmonary aspergillosis; treatment with prednisone (≥15 mg/day); the culture of a mycobacterial species from the sputum sample submitted at the screening visit or previous use of inhaled colistin. Patients prescribed other inhaled antibiotics were eligible for the study if they discontinued treatment at the screening visit. Patients prescribed a stable dose of azithromycin for ≥6 months were eligible for the study.			days) in the placebo group (P=0.038). Post-hoc analysis of patients with ≥ 80% adherence: 27 of 54 (50%) in colistin group had an exacerbation vs. 39 of 54 (72%) in the placebo group. Median time (25% quartile) to exacerbation was 168 days (65 days) in the colistin group vs. 103 days (37 days) in the placebo group (P=0.028). **Severity of exacerbation:** Exacerbations treated with antibiotics: 75% colistin group and 79% placebo group (in the ITT population) (need for oral antibiotics classed as moderate exacerbation whereas intravenous antibiotics was classified as severe exacerbation) – does not state whether the remainder were treated with IV antibiotics or did not require antibiotics. **P. *aeruginosa* bacterial density (colony forming unit) (CFUs):** inhaled colistin: significant reductions in P.*aeruginosa* bacterial density after 4 and 12 weeks treatment	

					compared with placebo (-1.7 [2.2] vs. -0.3 [1.9] log_{10} CFU/g, P= 0.008, at 12 weeks) (ITT population). **24 hour sputum weight:** Mean (SD) change in 24-hour sputum weight from baseline to week 4 -3.6 g (22.4) in the colistin group vs -1.6g (9.9) in the placebo group (in ITT population). Estimated mean treatment difference -1.9 (95% CI, -8.3 to 4.5; P=0.56). **St George's Respiratory Questionnaire (SGRQ) total score:** colistin group: mean (SD) change in SGRQ total score from baseline to week 12 and week 26 of -2.8 (14.5) and -10.4 (19.6) units, respectively vs. placebo group; -2.2 (10.5) and -0.4 (13.2) units respectively. Estimated mean treatment differences in change in SGRQ total score from baseline to week 12 and week 26 -1.09 (95% CI, -5.18 to 2.99) and -10.51 (95% CI, -17.87 to -3.14), respectively. P=0.006 at week 26 **Bronchoconstriction in**	

					the 30 minutes post first dose of the study drug: Placebo group: 1 patient had a reduction in FEV_1 of ≥ 15% within 30 minutes of the first dose and discontinued treatment. Colistin group: 5 (7%) patients developed bronchoconstriction leading to discontinuation of treatment. **FEV_1:** Mean (SD) changes from baseline to Weeks 4, 12 and 26 in FEV_1 (L): colistin group: 0.03 (0.40), 0.01 (0.43) and -0.10 (0.45), respectively. Placebo group: 0.02 (0.18), -0.09 (0.34) and 0.00 (0.26), respectively. Estimated mean treatment differences in change in FEV_1 (L) from baseline to weeks 4, 12 and 26 were -0.05 (95% CI, -0.17 to 0.07), and -0.1 (95% CI, -0.22 to 0.02), respectively. Treatment differences not statistically significant. **Sensitivity of *P. aeruginosa* to colistin:** No colistin-resistant strains identified during the study. **CFUs of other potentially pathogenic**	

					microorganisms: No significant differences in treatment-emergent pathogens between treatment groups. **Adverse event reporting:** 143 AEs were reported in 47 (64%) patients in the colistin group. 108 AEs in 38 (54%) patients in the placebo group (p=0.25). 3 deaths were reported (considered unlikely to be related to the study drug by an investigator). 1 death (cardiopulmonary failure) occurred in the colistin group and 2 deaths (bronchiectasis and respiratory failure and ACS) occurred in the placebo group.	
Footnotes						

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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