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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Colistin for Prophylactic Use in Non-Cystic Fibrosis Bronchiectasis or COPD with Exacerbations: A Review of Clinical and Cost-Effectiveness and Guidelines

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Chronic obstructive pulmonary disease (COPD) which includes chronic bronchitis and emphysema, is a leading cause of morbidity and mortality in Canada, with a national estimate of COPD prevalence of approximately 4% in 2011.[1] Patients with COPD can experience exacerbations, or periods of worsening of COPD symptoms such as increased breathlessness, tiredness, fever and change in sputum colour. Bronchiectasis, or dilatation of the airways due to infective causes or cystic fibrosis (CF), had an incidence of 272 per 100 000 in those over 75 years of age in the US as of 2005.[2] The reduced ability to clear secretions from dilated airways eventually leads to airway blockage and loss of lung function.

A variety of preventive antibiotic regimens have been used to reduce the frequency of exacerbations and prevent further loss of lung function in patients with non-CF bronchiectasis or COPD, including amikacin, ciprofloxacin, gentamicin, colistin or tobramycin when *Pseudomonas aeruginosa* or other bacteria are present in the respiratory secretions.[3,4] Colistin belongs to the polymyxin group of antibiotics. It was first isolated in Japan in 1949, and is a bactericidal drug that has a narrow antibacterial spectrum and is primarily used for infections with *P. aeruginosa* and *Acinetobacter baumannii*.[5] Because of the concern of resistance development associated with newer antibiotics such as ciprofloxacin, colistin has been increasingly prescribed in bronchiectasis and COPD with exacerbations.[3,6] Inhaled formulations of antibiotics used in non-CF and COPD can reduce the systemic side-effects of oral drugs but may cause significant bronchial irritation leading to bronchospasm.[7]

This Rapid Response report aims to review the clinical effectiveness of colistin for the prevention of progression of bacterial colonization in adults with non-CF bronchiectasis or patients with COPD experiencing exacerbations. Cost-effectiveness and evidence-based guidelines associated with the use of colistin for the prophylactic treatment of adults with either non-CF bronchiectasis or patients with COPD experiencing exacerbations will also be examined.

Research Question

1. What is the clinical effectiveness of colistin for the prophylactic treatment of adults with either non-cystic fibrosis bronchiectasis or patients with chronic obstructive pulmonary disease experiencing exacerbations?
2. What is the cost-effectiveness of colistin for the prophylactic treatment of adults with either non-cystic fibrosis bronchiectasis or patients with chronic obstructive pulmonary disease experiencing exacerbations?
3. What are the evidence-based guidelines associated with the use of colistin for the prophylactic treatment of adults with either non-cystic fibrosis bronchiectasis or patients with chronic obstructive pulmonary disease experiencing exacerbations?

Key Findings

Indirect comparisons from a systematic review between inhaled antibiotics colistin, ciprofloxacin, and the aminoglycosides tobramycin and amikacin showed that ciprofloxacin

is more efficient than colistin and aminoglycosides in reducing sputum bacterial load in patients with stable non-cystic fibrosis bronchiectasis. Inhaled aminoglycosides tobramycin, amikacin and gentamicin significantly increased the risk of bronchospasm while inhaled ciprofloxacin and colistin were not significantly associated with the occurrence of this adverse event. A head-to-head comparison between inhaled colistin and tobramycin showed similar results in the number of hospital admissions due to exacerbations, duration of hospitalizations, and adverse events. Emergence of resistance to colistin was lower than resistance to tobramycin. There was no evidence found on patients with COPD experiencing exacerbations. There was no evidence found on cost-effectivenessor evidence-based guidelines regarding the use of colistin for the prophylactic treatment of adults with either non-CF bronchiectasis or patients with COPD experiencing exacerbations.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. The search was limited to English language documents published between Jan 1, 2007 and Jun 1, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adults in the community setting with either non-CF bronchiectasis or patients with COPD experiencing exacerbations; may or may not have colonization and/or infection
Intervention	Colistin, colistimethate (brand name Coly-Mycin) for prophylactic use
Comparator	Q1-2: Chronically used inhaled antibiotics (e.g., tobramycin, gentamycin, Quisair); chronically used oral antibiotics; lung resection surgery Q3: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., for prophylaxis of infection, prevention of exacerbations, reduction in exacerbations, improved quality of life, etc.) Q2: Cost-effectiveness (e.g., cost per QALY increased, cost per decrease in exacerbations, etc.) Q3: Guidelines
Study Designs	Heath technology assessments, systematic reviews, meta-analyses, RCTs, non-RCTs, cost studies

CF = cystic fibrosis; COPD = chronic obstructive pulmonary disease; RCT = randomized controlled trial; QALY = quality-adjusted life year.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, were already reported in the included systematic reviews, or were published prior to 2007.

Critical Appraisal of Individual Studies

The included systematic review and clinical studies were assessed using the AMSTAR[8] and Downs and Black[9] checklists, respectively. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 29 citations were identified in the literature search. Following screening of titles and abstracts, 23 citations were excluded and six potentially relevant reports from the electronic search were retrieved for full-text review. One potentially relevant publication was retrieved from the grey literature search. Of these potentially relevant articles, five publications were excluded for various reasons, while two publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The literature search identified one relevant systematic review[10] and one relevant clinical study.[11] Characteristics of the included studies are detailed in Appendix 2.

The 2014 systematic review[10] included 12 randomized controlled trials (RCTs) and performed meta-analysis from eight RCTs that compared inhaled antibiotics (colistin, tobramycin, amikacin, ciprofloxacin) to placebo in 590 adult patients with stable non-CF bronchiectasis. Treatment duration in the RCTs ranged from four weeks to 12 months. The main objective of the systematic review was to compare inhaled antibiotics to placebo. Outcomes from subgroup analyses comparing different types of antibiotics were used for this review. There were no head-to-head trials between different antibiotics; the comparison between colistin and other antibiotics was an indirect comparison. Outcomes reported were sputum bacterial load reduction and adverse events such as bronchospasm. The systematic review was conducted by authors from UK and Brazil.

The 2011 clinical study[11] is a prospective observational cohort study that compared efficacy and harms of inhaled colistin to inhaled tobramycin in 81 adult patients with non-cystic fibrosis bronchiectasis after at least 12 weeks of treatment. Primary outcomes reported were frequency and duration of hospitalizations for respiratory exacerbations. The study was conducted in Spain.

Summary of Critical Appraisal

The included systematic review[10] provided an a priori design and performed a comprehensive literature search. Procedures for the independent duplicate selection and data extraction of the study were in place, a list of included studies and characteristics were provided, and quality assessment was used in formulating conclusions. The review did not

assess publication bias and did not include a list of excluded studies. There was a lack of information on random sequence generation and allocation concealment in most included trials, leading to concerns regarding potential selection bias. Pooling of data for some outcomes may have been inappropriate due to possible heterogeneity among RCTs included in the review, such as variation in treatment duration. The systematic review included only patients with stable non-CF bronchiectasis, and many trials excluded patients with comorbid conditions common to bronchiectasis such as immune deficiency, mycobacterium infections, thus limiting the representativeness of the study samples and the generalizability of findings.

The included clinical study[11]had a clearly reported hypothesis, method of selection from the source population and study population appeared to be representative of the source population. The main outcomes, interventions, patient characteristics, and main findings were clearly described, and estimates of random variability and actual probability values were provided. A power calculation was provided, and the study had sufficient power to detect a clinically important effect. The study was observational in design, and patients were not randomized leading to potential selection bias.

Details of the critical appraisal of the included studies are presented in Appendix 3.

Summary of Findings

The main findings of the included studies are presented in Appendix 4.

1. *What is the clinical* effectiveness *of colistin for the prophylactic treatment of adults with either non-CF bronchiectasis or patients with COPD experiencing exacerbations?*

The systematic review[10] performed meta-analysis from RCTs that compared inhaled antibiotics to placebo in adult patients with stable non-cystic fibrosis bronchiectasis. Outcomes from subgroup analyses comparing different types of antibiotics were used for this review. It is noteworthy that there was no head-to-head trial between antibiotics; the comparisons between antibiotics are indirect comparisons.

After four weeks of treatment, treatment with colistin, aminoglycosides, or ciprofloxacin was associated with a reduction in sputum bacterial load compared with placebo; however, the difference between aminoglycosides and placebo was not statistically significant. The largest reduction relative to placebo was observed with ciprofloxacin and the smallest reduction was observed with colistin. The authors concluded that ciprofloxacin is more effective than aminoglycosides and colistin in reducing sputum bacterial load.

Inhaled aminoglycosides significantly increased the risk of bronchospasm while inhaled ciprofloxacin and colistin were not significantly associated with the occurrence of this adverse event. The increase in risk of bronchospasm was smallest with ciprofloxacin, and similar between colistin and aminoglycosides.

The clinical study[11]compared the efficacy and harms of inhaled colistin to inhaled tobramycin in adult patients with non-CF bronchiectasis.There were no significant differences found between colistin and tobramycin in the mean number of hospital admissions, duration of hospitalizations, duration of antibiotic treatment, adverse events, mortality, or emergence of other opportunistic microorganisms. Emergence of resistance to colistin was lower than resistance to tobramycin, and the difference was statistically significant. The authors concluded that results with colistin were similar to those with tobramycin for inhaled treatment of *P. aeruginosa* in this population.

2. *What is the cost-effectiveness of colistin for the prophylactic treatment of adults with either non-CF bronchiectasis or patients with COPD experiencing exacerbations?*

There was no evidence found on the cost-effectiveness of colistin for the prophylactic treatment of adults with either non-CF bronchiectasis or patients with COPD experiencing exacerbations.

3. *What are the evidence-based* guidelines *associated with the use of colistin for the prophylactic treatment of adults with either non-CF bronchiectasis or patients with COPD experiencing exacerbations?*

There was no evidence found on the evidence-based guidelines associated with the use of colistin for the prophylactic treatment of adults with either non-CF bronchiectasis or patients with COPD experiencing exacerbations.

Limitations

As mentioned in the quality appraisal of the included studies, comparison between different antibiotics in the systematic review is indirect, with no head-to-head comparison; there is also concern on the representativeness of the study samples and generalizability of the findings since patients with unstable conditions or comorbidities were excluded. There may be potential selection bias in the systematic review. The included clinical trial is observational by nature; prospective, double-blind, head-to-head RCTs are needed to confirm the efficacy of colistin compared with other antibiotics for the treatment of non-CF bronchiectasis. There was no evidence found on patients with COPD experiencing exacerbations.

Conclusions and Implications for Decision or Policy Making

Indirect comparisons between inhaled antibiotics colistin, ciprofloxacin, tobramycin and amikacin suggested that ciprofloxacin is more efficient than colistin and aminoglycosides in reducing sputum bacterial load in patients with stable non-CF bronchiectasis. Inhaled aminoglycosides tobramycin, amikacin and gentamicin significantly increased the risk of bronchospasm relative to placebo, while inhaled ciprofloxacin and colistin were not significantly associated with the occurrence of this adverse event. Inhaled colistin and tobramycin showed similar efficacy results in an observational study, with lower emergence to resistance to colistin than to tobramycin.

Prospective, double-blind, head-to-head RCTs are needed to confirm the efficacy of colistin compared with other antibiotics for the treatment of non-CF bronchiectasis or patients with COPD experiencing exacerbations. Cost-effectiveness studies regarding the use of colistin for the prophylactic treatment of adults with either non-CF bronchiectasis or patients with COPD experiencing exacerbations are also needed to formulate evidence-based guidelines for the use of colistin.

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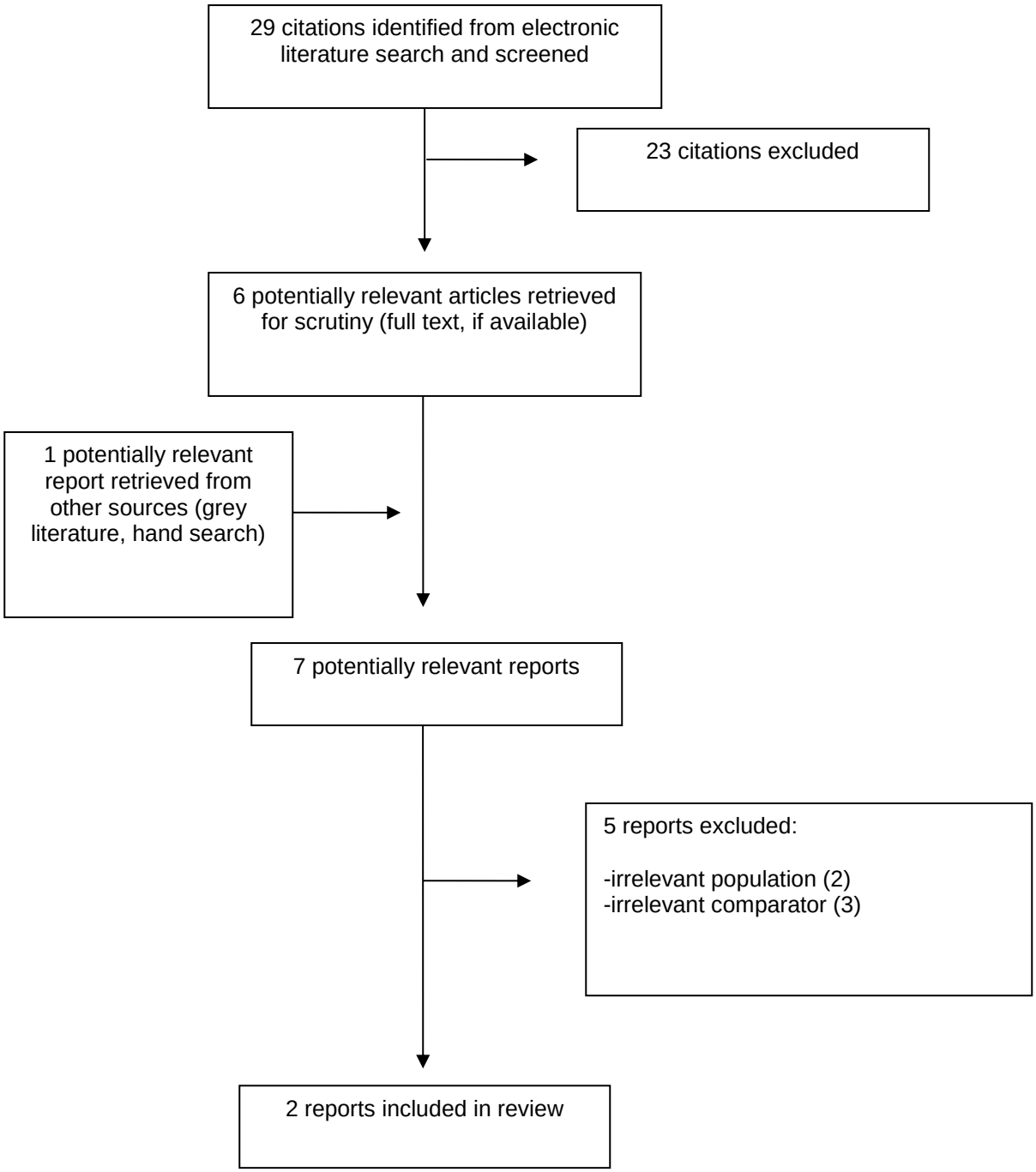
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table A1: Characteristics of Included Systematic Review

First Author, Year, Country	Objectives Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Number of studies included Main Outcomes
Brodt,[10] 2014, Brazil, UK	*"We conducted a meta-analysis of randomised trials to evaluate the efficacy and safety of inhaled antibiotics in patients with stable non-cystic fibrosis (CF) bronchiectasis" (p 382)* *"We searched the Cochrane Airways Group Register of Trials from inception until March 2014" (p 382)*	*"1) Study design: a randomised controlled trial. 2) Participants: adult or paediatric patients with bronchiectasis diagnosed by bronchography or computed tomography, and in a stable clinical condition. 3) Interventions and comparisons: antibiotics administered via inhalation for ≥ 4 weeks, compared with placebo or other interventions. 4) Outcomes (at least one of the following measures was obtained): sputum analysis (microbiological examination and/or physical properties), clinical response, acute exacerbations, hospital admission, pulmonary function test, health-related quality of life, markers of airways and systemic inflammation, and safety" (p 383)*	*"Trials were excluded if patients had a diagnosis of CF or other chronic pulmonary disorders, or had an acute exacerbation at study entry" (p 383)*	12 trials (1264 adult patients) included for the review 8 trials (590 patients) included for the meta-analysis *Efficacy:* Change in sputum bacterial load (calculated as colony-forming unit log10 CFU.g^{-1},a measure of viable bacterial or fungal cells) *Adverse events:* Bronchospasm

Table A2: Characteristics of Included Clinical Studies

First Author, Year, Country	Study Design Study Objectives	Interventions/ Comparators	Patients	Main Outcomes
Berlana,[11] 2011, Spain	Prospective, observational cohort study *"To compare clinical and microbiologic outcomes in adults without cystic fibrosis who had Pseudomonas aeruginosa bronchial colonization and were receiving inhaled colistin or colistin plus tobramycin with those who were receiving inhaled tobramycin as outpatient treatment"* (p 146)	Inhaled colistin alone Inhaled colistin + tobramycin Inhaled tobramycin	81 adult patients receiving 97 courses of inhaled antibiotics for at least 12 weeks	*Primary outcomes*: Frequency and duration of hospitalizations for respiratory exacerbations *Secondary outcomes:* Emergence of bacterial resistance, antibiotic use during admission, emergence of other opportunistic microorganisms, and mortality, as well as safety and changes in respiratory function.

Appendix 3: Critical Appraisal of Included Publications

Table A3: Strengths and Limitations of Clinical Systematic Reviews using AMSTAR[8]

Strengths	Limitations
Brodt, 2014[10]	
• a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, studies characteristics provided • quality assessment of included studies provided and used in formulating conclusions • conflict of interest stated	• list of excluded studies not provided • assessment of publication bias not performed

Table A4: Strengths and Limitations of Clinical Studies using Downs and Black[9]

Strengths	Limitations
Berlana, 2011[11]	
• hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided • study had sufficient power to detect a clinically important effect	• observational study design, patients not randomized

Appendix 4: Main Study Findings and Author's Conclusions

Table A5: Summary of Findings of Included Clinical Studies

Main Study Findings	Author's Conclusion
Brodt, 2014[10]	
Reduction of bacterial load at 4 weeks compared to placebo (WMD; log10 CFU.g^{-1}) Colistin: -1.40 (95% CI -2.07 to -0.73) (bacteria: PA; data from 1 trial on 144 patients) Aminoglycosides (tobramycin, amikacin): -2.45 (95% CI -6.55 to 1.64) (bacteria: PA; data from 2 trials on 123 patients) Ciprofloxacin: -3.52 (95% CI -4.64 to -2.40) (bacteria: PA; data from 2 trials on 122 patients) P = 0.006 for all comparisons *Adverse events: Bronchospasm compared to placebo (RR)* Colistin: 4.86 (95% CI 0.58 to40.59, *P* = 0.14) (data from 1 trial on 144 patients) Ciprofloxacin: 1.07 (95% CI 0.25 to 4.56, *P* = 0.93) (data from 2 trials on 166 patients) Tobramycin, gentamycin, amikacin: 4.78 (95% CI 1.55 to14.76, *P* = 0.007) (data from 4 trials on 216 patients)	*"Subgroup analysis shows that ciprofloxacin is more effective than aminoglycosides and colistin in reducing sputum bacterial density" (p 390)* *"The subgroup analysis showed that inhaled aminoglycosides significantly increased the risk of bronchospasm while inhaled ciprofloxacin and colistin were not significantly associated with the occurrence of this adverse event" (p 389)*
Berlana, 2011[11]	
Efficacy Number of hospital admissions Colistin: 2.0 ± 2.6 Tobramycin: 1.3 ± 1.8 Duration of hospitalization (days) Colistin: 23.9 ± 29.5 Tobramycin: 16.4 ± 22.0 Duration of antibiotic use (days) Colistin: 19.3 ± 24.9 Tobramycin: 11.0 ± 14.5 Adverse events: Colistin: 29/50 patients (58%) Tobramycin: 20/72 (28%) Mortality: 12 patients (14.8%) died; no significant differences	*"No significant differences between colistin and tobramycin were found in the mean number of hospital admissions, duration of hospitalizations, duration of antibiotic treatment, adverse events, mortality, or emergence of other opportunistic microorganisms. Emergence of resistance to colistin was lower than resistance to tobramycin" (p 146)*

Main Study Findings	Author's Conclusion
between the study groups (number per group not reported) Emergence of other opportunistic microorganisms (number of treatments): Colistin: 9/29 (31%) Tobramycin: 15/49 (31%) Emergence of resistance to colistin: lower than resistance to tobramycin (HR 0.09; 95% CI 0.03 to 0.32; *P*< 0.01)	

CFU = colony forming unit; HR = hazard ratio; PA = *Pseudomonas aeruginosa*; RR = risk ratio; WMD = weighted mean difference.