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Prophylactic Antibiotics for Individuals With Chronic Obstructive Pulmonary Disease (COPD): A Rapid Review

Health Quality Ontario

February 2015

Evidence Development and Standards Branch at Health Quality Ontario

Prophylactic Antibiotics for Individuals With Chronic Obstructive Pulmonary Disease (COPD): A Rapid Review. February 2015; pp. 1–26

Suggested Citation

This report should be cited as follows:

Health Quality Ontario. Prophylactic antibiotics for individuals with chronic obstructive pulmonary disease (COPD): a rapid review. Health Quality Ontario; 2015 February. 26 p. Available from: http://www.hqontario.ca/evidence/evidence-process/episodes-of-care#community-copd.

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Conflict of Interest Statement

All authors in the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Rapid Review Methodology

Rapid reviews must be completed in a 2- to 4-week time frame. Clinical questions are developed by the Evidence Development and Standards branch at Health Quality Ontario, in consultation with experts, end users, and/or applicants in the topic area. A systematic literature search is then conducted to identify relevant systematic reviews, health technology assessments, and meta-analyses. The methods prioritize systematic reviews, which, if found, are rated by AMSTAR to determine the methodological quality of the review. If the systematic review has evaluated the included primary studies using the GRADE Working Group criteria (http://www.gradeworkinggroup.org/index.htm), the results are reported and the rapid review process is complete. If the systematic review has not evaluated the primary studies using GRADE, the primary studies in the systematic review are retrieved and the GRADE criteria are applied to 2 outcomes. If no systematic review is found, then RCTs or observational studies are included, and their risk of bias is assessed. All rapid reviews are developed and finalized in consultation with experts.

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Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series,* which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

About Health Quality Ontario Publications

To conduct its rapid reviews, the Evidence Development and Standards branch and its research partners review the available scientific literature, making every effort to consider all relevant national and international research; collaborate with partners across relevant government branches; consult with expert advisory panels, clinical and other external experts, and developers of health technologies; and solicit any necessary supplemental information.

In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Disclaimer

This rapid review is the work of the Evidence Development and Standards branch at Health Quality Ontario, and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. As this is a rapid review, it may not reflect all the available scientific research and is not intended as an exhaustive analysis. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its rapid reviews. In addition, it is possible that other relevant scientific findings may have been reported since completion of the review. This report is current as of the date of the literature search specified in the Research Methods section. Health Quality Ontario makes no representation that the literature search captured every publication that was or could be applicable to the subject matter of the report. This rapid review may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

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List of Abbreviations

AMSTAR	Assessment of Multiple Systematic Reviews
AZM	Azithromycin
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
FEV_1	Forced expiratory volume in 1 second
GI	Gastrointestinal
GOLD	Global Initiative for Chronic Obstructive Lung Disease
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
MD	Median days
NNT	Number needed to treat
NNH	Number needed to harm
OR	Odds ratio
OHTAC	Ontario Health Technology Advisory Committee
QBP	Quality-Based Procedure
RCT	Randomized controlled trial
RR	Relative risk
SR	Systematic review

Background

As legislated in Ontario's *Excellent Care for All Act*, Health Quality Ontario's mandate includes the provision of objective, evidence-informed advice about health care funding mechanisms, incentives, and opportunities to improve quality and efficiency in the health care system. As part of its Quality-Based Procedures (QBP) initiative, Health Quality Ontario works with multidisciplinary expert panels (composed of leading clinicians, scientists, and administrators) to develop evidence-based practice recommendations and define episodes of care for selected disease areas or procedures. Health Quality Ontario's recommendations are intended to inform the Ministry of Health and Long-Term Care's Health System Funding Strategy.

For more information on Health Quality Ontario's Quality-Based Procedures initiative, visit www.hqontario.ca.

Objective of Analysis

The objective of this analysis was to assess the effectiveness and safety of the prophylactic use of the antibiotic azithromycin (AZM) for COPD patients who are at increased risk of future exacerbations.

Clinical Need and Target Population

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory condition of irreversible airflow limitation. (1) An inflammatory disease, it fluctuates from periods of stability to periods of acute worsening (exacerbation) where interventions and hospitalization may be required to improve airflow. (1) Antibiotics are one intervention with demonstrated effectiveness for treating COPD exacerbations where there is evidence of infection (e.g., purulent sputum). (2) However, their role in preventing exacerbations, especially among patients who have frequent exacerbations despite optimal therapy, is poorly understood.

Technology/Technique

There are many classes of antibiotics, including beta-lactams (e.g., penicillin), tetracyclines (e.g., doxycycline), quinolones (e.g., moxifloxacin), and macrolides (e.g., azithromycin [AZM]). (3) The latter type have demonstrated antimicrobial effectiveness for the treatment of respiratory infections, (4) and also exert immunoregulatory actions that restrict the destruction of lung tissue by key immune-system cells. (2)

Macrolide maintenance therapy became standard care for patients with diffuse panbronchiolitis (a severe progressive inflammatory lung disease affecting small air passages) in the late 1980s. This was prompted after it was observed to result in a dramatic decrease in symptoms and increase in survival (i.e., a 60% to 70% increase in 10-year survival). (2) Randomized controlled trials (RCTs) investigating macrolide maintenance therapy with AZM to treat cystic fibrosis (another chronic inflammatory respiratory disease) have shown significant improvements in lung function, physical condition, and weight gain, and decreases in the frequency of infectious exacerbations. (5) Maintenance (i.e., prophylactic) doses of antibiotics tend to be lower than the doses needed to treat an acute infection, but adverse effects of prolonged antibiotic therapy are of great concern. This is true at both the patient level (e.g., AZM-associated hearing impairment) and at the societal level, with concerns about antibiotic resistance. The evidence for the effectiveness and safety of the prophylactic use of macrolides in COPD has been mixed. (5) To our knowledge, a systematic evidence review synthesizing studies on AZM alone has yet to be undertaken.

Rapid Review

Research Question

What is the effectiveness and safety of the prophylactic use of the antibiotic azithromycin (AZM) for COPD patients who are at increased risk of future exacerbations?

Research Methods

Literature Search

Search Strategy

A literature search was performed on July 4, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, and EBM Reviews, for studies published from January 1, 2009, to July 4, 2014. (Appendix 1 provides details of the search strategies.) Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2009, and July 4, 2014
- health technology assessments, systematic reviews (SRs), and meta-analyses
- studies evaluating prophylactic use of antibiotics
- studies on adult, stabilized COPD patients
- azithromycin (AZM) results reported separately

Exclusion Criteria

- RCTs, observational studies, case series, editorials, conference abstracts
- studies on populations other than COPD (e.g., tracheostomy, cystic fibrosis)
- studies evaluating antibiotic treatment during an acute exacerbation of COPD
- studies reporting only on classes of antibiotics or all antibiotics in aggregate

Outcomes of Interest

- effect on exacerbations
- adverse events (i.e., gastrointestinal side effects, hearing, and antibiotic resistance)

Expert Panel

In November 2013, an Expert Advisory Panel on Post-Acute Community-Based Care for COPD Patients was struck. Members of the panel included physicians, personnel from the Ministry of Health and Long-Term Care, and representatives from community care organizations.

The role of the expert advisory panel was to provide advice on primary COPD patient groupings; to review the evidence, guidance, and publications related to defined COPD patient populations; to identify and prioritize interventions and areas of community-based care; and to advise on the development of a care pathway model. The role of panel members was to provide advice on the scope of the project, the methods used, and the findings. However, the statements, conclusions, and views expressed in this report do not necessarily represent the views of the expert panel members.

Quality of Evidence

The Assessment of Multiple Systematic Reviews (AMSTAR) measurement tool was used to assess the methodological quality of systematic reviews. (6)

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria. (7) The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Study design was the first consideration; the starting assumption was that randomized controlled trials (RCTs) are high quality, whereas observational studies are low quality. Five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias—were then taken into account. Any limitations in these areas resulted in downgrading the quality of evidence. Finally, 3 main factors that may raise the quality of evidence were considered: the large magnitude of effect, the dose response gradient, and any residual confounding factors. (7) For more detailed information, please refer to the latest series of GRADE articles. (7)

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect.
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different.
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect.
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect.

Results of Rapid Review

The database search yielded 262 citations published between January 1, 2009, and July 4, 2014 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

Four systematic reviews (SRs) met the inclusion criteria (8-11) and received AMSTAR scores of 10, 8, 8, and 7, respectively. We selected the SR by Herath and Poole for inclusion in this rapid review because of its superior quality as assessed by AMSTAR, and because it had the most comprehensive search. It captured the same RCTs on AZM in COPD populations as were captured in the other 3 SRs, as well as

recent literature, both published and unpublished. The reference list of the included SR and health technology assessment websites were hand-searched to identify other relevant studies, and no additional citations were identified.

The SR by Herath and Poole (8) is an update to another Cochrane review, done in 2003, on chronic bronchitis. Herath and Poole aimed to a) focus exclusively on COPD patients, and b) update the evidence of the effect on exacerbations, quality of life, and, secondarily, possible harms. Their search for eligible RCTs included literature up to August 2013. Although their review examined all classes of oral antibiotics, AZM was analyzed and results were reported separately, as available. Table 1 provides an overview of the AZM trials included in the review.

Table 1: Prophylactic Azithromycin Trials on COPD Patients Included in Systematic Review

Author, Year	Country	Intervention (n) Comparator (n)	Follow-up Period	Outcomes Reported
Albert et al, 2011 (12)	United States	AZM 250mg daily for 1 year (570) Placebo (572)	1 year	Time to first AE Frequency of AEs QOL Hearing impairment
Mygind et al, 2010 (13)[a]	Denmark	AZM 500mg 3 days every month for 36 months (287) Placebo (288)	3 years	Change in pulmonary function AE duration and frequency Hospital admissions QOL Mortality

Abbreviations: AE, acute exacerbation of COPD; AZM, azithromycin; COPD, chronic obstructive pulmonary disease; n, number; QOL, quality of life.
[a]Trial information included in the review is based on unpublished data presented at a conference.
Source: Herath and Poole, 2013. (8)

The 2 AZM trials were conducted on moderate to severe COPD patients (i.e., with forced expiratory volume in 1 second [FEV_1] < 70%), who, within the previous year, had at least 1 documented exacerbation OR emergency-department visit or hospitalization for exacerbation, OR used systemic corticosteroids, OR had continuous oxygen supplementation. Mygind and colleagues excluded patients whose life expectancy was shorter than the study duration, (13) both studies excluded patients with other significant respiratory conditions, and Albert and colleagues also excluded those at risk for cardiac conditions (e.g., with resting heart rate above 100 beats per minute). (12) In the study by Albert and colleagues, (12) about 80% of participants took AZM as an adjunct to inhaled therapy of glucocorticoids, a long-acting beta2-agonist, a long-acting muscarinic agent, or any combination of the above. In both studies, all participants were 40 years of age or older.

Effect on Exacerbations

As seen in Table 1, the 2 RCTs reported the effect of AZM on COPD exacerbations via slightly different outcomes. Thus, in the SR, outcome was reported separately for each RCT. The primary outcome for Albert and colleagues (12) was time to first exacerbation (median days [MD]), which was significantly longer for patients in the AZM group (266 days; 95% confidence interval [CI], 227–313) than for those who received a placebo (174 days; 95% CI, 143–215, $P < 0.001$). The rate of exacerbations per patient-year was also significantly lower in the AZM group (1.48) compared with 1.83 in the placebo group (rate ratio, 0.83; 95% CI, 0.72–0.95, $P = 0.01$). The number of patients who would need to be treated (NNT) to prevent one exacerbation was 2.86. Reporting on the RCT by Albert and colleagues, SR authors Herath and Poole present the rate ratios of exacerbations, stratified by COPD severity, for patients at stage 2, 3,

and 4 per the Global Initiative for Chronic Obstructive Lung Disease (GOLD). The rates are 0.77, 0.89, and 0.72 per patient-year, respectively. The SR states that the data were inadequate to determine statistical significance for the rate ratios. (8)

The trial by Mygind and colleagues (13) analyzed duration of exacerbations and found that the number of days of exacerbation was significantly lower in the AZM group than in the placebo group (MD 93 versus MD 111, $P = 0.04$). They broke it down further, looking separately at home- and hospital-managed exacerbations, and also found a statistically significant reduction in days of severe exacerbation managed at home (MD 31 in the AZM group versus MD 42.5 in the placebo group, $P = 0.01$). A similarly shortened duration was found for hospital-managed exacerbations (a median hospital stay of 15.5 days for the AZM group versus 18 days for the placebo group). In this case, however, the authors did not provide a *P* value, so statistical significance cannot be determined.

Adverse Events

Overall, serious adverse events are poorly explained in this body of literature. Albert and colleagues (12) did not find any difference in the risk of gastrointestinal (GI) disorders between AZM and placebo groups (odds ratio [OR], 0.71; 95% CI, 0.36–1.39), though the overall event rate was low (AZM: 15 events, placebo: 21 events, $P = 0.38$). In contrast, Mygind and colleagues reported significantly more adverse lower-GI effects in the AZM group (513 versus 185 events, $P = 0.006$), with no difference in the number of upper-GI adverse effects or infections. (13)

Albert and colleagues found a significant increase in the risk of hearing impairment in the AZM group compared with the placebo group (OR, 1.39; 95% CI, 1.05–1.85), and reported that this, in the majority of cases, was the cause of the drug being discontinued. (12) Based on this study, the number of patients who would need to be treated to cause harm to one patient (NNH) was 18 (95% CI, 128–9). The study reported that hearing returned to baseline level in 25% to 38% of the participants in both study groups (see (12) for details). The authors speculate that their study overestimated the incidence of hearing decrements because of overly stringent eligibility criteria and audiometry measurement error.

The same study (12) included antibiotic resistance as a secondary outcome. Specifically, Albert and colleagues measured colonization at baseline (see Table 2) and again at follow-up, to see if more patients in the AZM group were colonized by macrolide-resistant organisms. If so, this could contribute to a macrolide-resistance problem. When organisms develop resistance to the antimicrobial effects of AZM and other macrolides, these drugs are no longer effective for preventing or treating infections. As therapy options become fewer, individual clinical outcomes are poorer, the infective phase can be prolonged, and resistant bacteria are allowed to spread across patients and populations. (14) The researchers used sputum organism analysis to evaluate the rates of bacterial colonization for the 2 groups, identifying the most common organisms via expectorated sputum when possible (in 15% of participants) and via nasopharyngeal swab in the remaining 85%. The results of evaluation at baseline are shown in Table 2.

Table 2: Most Common Organisms Identified at Baseline in Study Participants

Organisms	Number of Patients per Group		Number of Patients Colonized (%)	
	Intervention	Control	Intervention	Control
S. aureus	570	572	60 (10.7)	71 (12.7)
Moraxella spp.			13 (2.3)	6 (1.1)
S. pneumoniae			6 (1.1)	6 (1.1)

Abbreviations: *Moraxella* spp., *Moraxella* species; *S. aureus, Staphylococcus aureus*; *S. pneumoniae, Streptococcus pneumonia.*
Source: Albert et al, 2011. (12)

The authors speculated that the predominance of *S. aureus* in their study sample may be confounded by the use of nasopharyngeal sampling of patients in the 85% who could not expectorate sputum at the end of the treatment period.

The next finding—the results at follow-up—concerned patients who did not have existing bacterial colonization at baseline (i.e., those patients *not* in Table 2). Of these, the placebo group (n = 172) had a higher incidence rate of colonization by respiratory pathogens (i.e., rate of new colonization) at follow-up than did the AZM group (n = 66; $P < 0.001$). This statistically significant finding refers to colonization by any organism—macrolide-resistant or not—during the study period, and would generally be expected provided AZM is effective at killing bacteria. However, while less likely to have new colonization overall, those in the AZM group were more likely to have new colonization by macrolide-resistant organisms. This is also to be expected, given the natural history of how pathogens mutate and therefore develop resistance. In a both statistically and clinically significant finding, the incidence of macrolide resistance was significantly higher in the newly colonized AZM group than in the corresponding placebo group (81% versus 41%, $P < 0.001$).

Limitations

The body of evidence on the effectiveness and safety of AZM as a prophylactic intervention for COPD has limitations. The number of studies is small, with significant heterogeneity across studies. The RCT by Albert and colleagues (12) is cited as groundbreaking in this field due to its large size and resulting statistical power. However, 22 *a priori* subgroup analyses were conducted as part of that RCT, thus decreasing its statistical power to about 62%, as they were performed without statistical adjustment for multiple comparisons (resulting in a high risk of false positives). The results of the trial by Mygind and colleagues (13) were extracted by the SR authors from the abstract of a conference presentation of unpublished data which does not appear to have since been published. Herath and Poole report that their attempts to contact the authors were unsuccessful. Therefore, some important details of methodology (i.e., randomization) execution, and results are missing. Albert and colleagues, in their article, briefly discuss a case series on the topic of prophylactic AZM for COPD. However, this rapid review has been conducted without knowledge of other published observational or case-based literature, if any, which may exist. A full systematic review of primary studies is needed, to rigorously analyze and evaluate the entire body of contemporary evidence.

The GRADE quality assessment of the body of evidence on the effectiveness and safety of AZM for COPD exacerbation prophylaxis, based on the SR by Herath and Poole, can be found in Table A2 (Appendix 2).

Addendum to Rapid Review of Systematic Reviews

Herath and Poole (8) identified an RCT that was ongoing at the time of their review, which has since been published. (15) Given the knowledge of at least one trial and potentially others published since the SR, and given the gravity of the potential benefits and implications of long-term antibiotic therapy, it was determined that a supplemental search was warranted. A unique literature search was performed for published single RCTs comparing AZM with placebo in COPD patients in Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Embase, and EBM Reviews between January 1, 2013 and July 17, 2014 (see Appendix 1b). The 91 resulting citations were reviewed by a single author, who screened for RCTs but otherwise used identical inclusion and exclusion criteria as detailed on page 8.

Two single RCTs, both conducted in the Netherlands, met the inclusion criteria. (15, 16) Uzun and colleagues' study, the study identified as ongoing in the Herath and Poole SR, evaluated 500mg of AZM,

3 times per week for 1 year, in patients 18 years or older who had 3 or more exacerbations in the previous year. (15) In this study, 92 patients at a single centre were randomized to AZM (n = 47) or placebo (n = 45) in order to assess the rate of exacerbations over 12 months (per patient-year) and, secondarily, to assess the rate of adverse events, side effects, and macrolide resistance. The results of these outcomes are in Table 3.

Table 3: Prophylactic AZM Versus Placebo for COPD Patients—Results on Primary and Secondary Outcomes of Interest from an RCT

Outcome	Measurement Reported	Azithromycin	Placebo	*P* Value
Exacerbation rate (unadjusted)	rate ratio per patient-year	0.60 (95% CI: 0.43–0.84)		0.003
Exacerbation rate (adjusted[a])	rate ratio per patient-year	0.58 (95% CI: 0.42–0.79)		0.001
Time to first exacerbation	median days	130 (95% CI: 28–323)	59 (95% CI: 31–87)	0.001
Gastrointestinal adverse events	n (%)	16	10	NR
Diarrhoea		9 (19%)	1 (2%)	0.015
Nausea or vomiting		3 (6%)	2 (4%)	NR
Other		4 (9%)	7 (16%)	NR
Acquisition of macrolide-resistant bacteria[b]	n (%)	3 (6%)	11 (24%)	0.036

Abbreviations: AZM, azithromycin; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; n, number of patients; NR, not reported; RCT, randomized controlled trial.
[a]Covariates adjusted for: use of low-dose long-term prednisolone, number of exacerbations in previous year, age, sex, smoking, and FEV_1.
[b]Sputum samples were obtained and analyzed from only a subset of 42 participants.
Source: Uzun et al, 2014. (15)

The exacerbation rate over 12 months was significantly lower in the AZM group compared with the placebo group, and was nearly identical after adjusting for relevant covariates. In terms of adverse events, diarrhoea was significantly more common in the AZM group. Interestingly, more patients taking placebo acquired macrolide-resistant bacteria, compared with those taking AZM. (15) This finding could not be explained by the authors and, in contrast to the macrolide-resistance finding by Albert and colleagues, it is the opposite of what would be expected. No audiometry was performed, and no formal results presented regarding hearing impairment. However, the authors stated that 1 participant receiving placebo reported hearing loss at the end of the study. (15) The authors highlight important differences between their study and the one conducted by Albert and colleagues in terms of methodology, inclusion criteria, participant characteristics, and drug regimen; they caution against direct comparison of the 2 studies. Uzun and colleagues' study population had a larger representation of females, and stricter exclusion of participants with bronchiectasis, a condition for which AZM is known to be effective, and whose inclusion may, therefore, confound the results.

In the second RCT that met our inclusion criteria, Berkhof and colleagues had a primary focus on cough-specific quality of life in COPD patients at GOLD stage 2 or higher, aged 40 years and older, with chronic productive cough. (16) Participants (n = 84) were randomized to receive a placebo or 250mg of AZM 3 times per week for 12 weeks, with follow-up extending to 18 weeks. (16) As secondary outcomes, time to first exacerbation, adverse events, and global measurement of colonization with respiratory pathogens were reported (see Table 4 for results).

Table 4: Prophylactic AZM Versus Placebo for COPD Patients—Results on Secondary Outcomes of Interest From an RCT

Outcome	Measurement Reported	Azithromycin	Placebo	*P* Value
Time to first exacerbation	20th percentile, days[a]	105 (SD = 30)	66 (SD = 21)	0.13
Gastrointestinal adverse events	n (%)	5 (11.9%)	6 (14.3%)	0.75
Colonization with respiratory pathogens at 12 weeks (all)	n (Δ from baseline)	5[b] (-13)	18[c] (0)	NR

Abbreviations: AZM, azithromycin; COPD, chronic obstructive pulmonary disease; n, number of patients; NR, not reported; RCT, randomized controlled trial; SD, standard deviation.

[a]Percentile time calculated because less than 25% of the patients in the azithromycin group had an exacerbation during the 18-week follow-up period.

[b]One participant developed colonization by azithromycin-resistant *Haemophilus influenzae* bacteria at 12 weeks.

[c]One participant had colonization with azithromycin-resistant *Staphylococcus aureus* bacteria at baseline, but not at 12 weeks.

Source: Berkhof et al, 2013. (16)

Berkhof and colleagues found no difference in time to first exacerbation—a finding which must be considered in the context that a very small number of events occurred over the potentially too-short follow-up period (Table 4, footnote a). Similar to Mygind and colleagues, they found no difference in adverse events between groups; and their study, in line with the others identified in this review, observed a reduction in respiratory pathogen colonization among participants taking AZM. (16)

The findings from the SR by Herath and Poole (8) and from the 2 RCTs in this addendum (15, 16) are limited in comparability in terms of:

- AZM administration: 4 different regimens and treatment periods. The Expert Panel advised that, while 3 dosages per week will unlikely differ significantly from daily administration (due to the long half-life of AZM), a drug regimen of 3 days per month (Mygind et al (13)) is clinically different and, moreover, unlikely to be sufficient for effectiveness.
- Follow-up time: This ranged from as short as 18 weeks to 3 years (median: 12 months), leaving long-term effects unknown.
- Clinical characteristics: To combine the 4 study populations would be challenging. The Expert Panel advised that 1 or more exacerbations in a year would capture the vast majority of patients, but those with 3 or more exacerbations in a year, and those with chronic productive cough, are distinct subsets of COPD patients.
- Sample size: Most of the studies were adequately powered for primary outcomes. However, they likely lack sufficient group sizes and/or event rates for statistical comparison of subgroup or secondary analyses, especially of adverse events.
- Outcomes of interest: These were measured using different units of analysis, thus precluding statistical synthesis.
- Antibiotic-resistance measurement: Sputum analysis was conducted on a subset of the study populations, and acquired via different methods (i.e., expectorated sputum versus nasopharyngeal swab).

In light of heterogeneity in study populations and outcome measures, the Health Quality Ontario Rapid Review methodology for primary studies includes a risk of bias assessment based on GRADE Working Group criteria (7) to assess quality of evidence. Risk of bias is evaluated based on consideration of allocation concealment, blinding, complete accounting of patients and outcome events, selective reporting bias, and other limitations. Risk of Bias for the Uzun (15) and Berkhof (16) RCTs can be found in Table A4 (Appendix 3).

Conclusions

The evidence yielded mixed results on the effectiveness and safety of the prophylactic use of the antibiotic azithromycin (AZM) for COPD patients.

From the examination of 1 systematic review of RCTs (in Rapid Review, proper):

- Compared with placebo, prophylactic treatment with AZM in moderate to severe COPD patients at increased risk of future exacerbations significantly:
    - increased time to first exacerbation (GRADE quality of evidence: Moderate)
    - decreased the frequency of exacerbations (GRADE: Moderate)
    - shortened the duration of exacerbations (GRADE: Low)
- Compared with placebo, prophylactic treatment with AZM in moderate to severe COPD patients at increased risk of future exacerbations was associated with significant occurrence of adverse events, including:
    - GI adverse events (GRADE: Very low)
    - hearing impairment (GRADE: Moderate)
    - increased likelihood of colonization with macrolide-resistant organisms (i.e., increased risk of macrolide resistance) (GRADE: Moderate)

From the examination of 2RCTs (in addendum to Rapid Review):

- Based on a single RCT conducted on COPD patients who had experienced 3 or more exacerbations in the previous year, prophylactic AZM therapy compared with placebo:
    - increased the time to first exacerbation
    - reduced the frequency of exacerbations
    - increased the likelihood of diarrhoea
    - *reduced* the likelihood of colonization with macrolide-resistant organisms (i.e., reduced risk of macrolide resistance), for which no explanation was provided
- Based on a single RCT conducted on COPD patients with chronic productive cough, no difference was found between the AZM and placebo groups in
    - effect on exacerbations
    - GI adverse events

The evidence showed both a general trend of beneficial effect on patients' COPD exacerbation rates and uncertainty around the risk of adverse events and antibiotic resistance associated with prophylactic AZM therapy.

Acknowledgements

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Health Quality Ontario's Expert Advisory Panel on Acute COPD Episode of Care

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Dr Eddy Fan	Mount Sinai Hospital	Critical Care Unit, Respirology
Dr Eric Hentschel	St. Mary's General Hospital	Medical Director of the Chest Program
Dr Lori Whitehead	St. Joseph's Healthcare Hamilton	Respirologist
Dr Rob McFadden*	St. Joseph's Healthcare London	Chair, Medical Advisory Committee Director, Quality of Medical Care
Dr Roger Goldstein*	West Park Healthcare Centre	Specialist, CAVC and Respiratory Rehabilitation
Lawrence Jackson*	Sunnybrook Health Sciences Centre	Clinical Coordinator, Veterans Centre, Department of Pharmacy

Panel Members	Affiliation(s)	Appointment(s)
Lorraine Leblanc	Ontario Lung Association	Patient Advocate
Mark McIntyre	Mount Sinai Hospital	Clinical Pharmacist
Ann Bartlett*	St. Joseph's Healthcare Hamilton	Nurse Coordinator, Respiratory Rehabilitation
Dr Andrea Gershon	Sunnybrook Health Sciences Centre	Scientist, Evaluative Clinical Sciences, Trauma, Emergency & Critical Care Research Program
Debbie Coutts	Trillium Health Partners	Coordinator, Pulmonary Rehabilitation Program
Elizabeth Hill	Kingston General Hospital	Nurse Practitioner, Chronic Obstructive Pulmonary Disease
Filomena Travassos*	Trillium Health Partners	Manager, Case Costing
Sandra Nelson	Mount Sinai Hospital	Clinical Practice Leader, Pharmacy
Dr Ian Fraser*	Toronto East General Hospital	Chief of Staff
Dr Stewart Pugsley*	St. Joseph's Healthcare Hamilton	Head of Service, Respirology

*Member actively participated in the Update and Integration COPD Expert Advisory Panel in Phase 3, which involved updating the acute episode of care and integrating it with the post-acute episode of care.

Health Quality Ontario's Expert Advisory Panel on Post-Acute Community-Based Care for COPD Patients

Panel Members	Affiliation(s)	Appointment(s)
Co-Chairs		
Dr. Chaim Bell	Mount Sinai Hospital University of Toronto	Clinician Scientist Associate Professor
Lisa Droppo	Ontario Association of Community Care Access Centers (OACCAC)	Chief Care Innovations Officer
Primary Care		
Dr. Kenneth Hook	Ontario College of Family Physicians STAR Family Health Team	Past-President Senior Physician
Dr. Alan Kaplan	Family Physicians Airway Group of Canada	Chair, Family Physicians Airway Group of Canada

Panel Members	Affiliation(s)	Appointment(s)
Dr. Peter Selby	Department of Family and Community Medicine & Psychiatry and Dalla Lana School of Public Health University of Toronto Ontario Tobacco Research Unit	Associate Professor Principal Investigator
Respirology		
Dr. Samir Gupta	St Michael's Hospital	Adjunct Scientist, Keenan Research Centre
Dr. Roger Goldstein	West Park Health Centre Toronto Rehabilitation Institute	Respiratory Division Head Associate Medical Staff Professor of Medicine
Respiratory Therapy		
Ivan Nicoletti	Erie St. Clair CCAC	Care Coordinator
Sara Han	Ontario Lung Association Mount Sinai Hospital	PCAP Provincial Coordinator Certified Respiratory Educator
Miriam Turnbull	ProResp Inc	General Manager
Madonna Ferrone	Erie St. Clair LHIN	Project Manager ARGI, Lung Health Collaboratist
Nursing		
Cheryl Lennox	South West Community CCAC, Intensive Home Care Team	Nurse Practitioner-Primary Health Care Certified Respiratory Educator
Andrea Roberts	Toronto Central CCAC	Rapid Response Transition Nurse
Mary-Jane Herlihey	ParaMed Home Health Care Ottawa	Clinical Consultant
Suzy Young	St. Mary's General Hospital	Nurse Practitioner Primary Health Care SWCCAC Intensive Health Care Team Certified Respirator Educator
Tanya Spencer Cameron	Family Health Team-Timmins	Nurse Practitioner
Physiotherapy		
Tania Janaudis-Ferreira	Sunnybrook Research Institute West Park Healthcare Centre	Scientist
Sheila Cameron	Champlain CCAC	Physiotherapist
Homecare		
Daniel Ball	Central West CCAC	Director of Client Services
Josie Barbita	Toronto Central CCAC	Director Professional Practice
Nutrition		
Darlene Mantione	Saint Elizabeth Health Care	Registered Dietitian

Panel Members	Affiliation(s)	Appointment(s)
Occupational Therapy		
Shirley Price	West Park Healthcare Centre	Manager, Rehab Plus Outpatient Services
Cardiovascular Services		
Kori Kingsbury	Cardiac Care Network	Chief Executive Officer

Appendices

Appendix 1a: Literature Search Strategy for Rapid Review

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 2014>, EBM Reviews - ACP Journal Club <1991 to June 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <May 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <2nd Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2014>, Ovid MEDLINE(R) <1946 to June Week 4 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 03, 2014>
Search Strategy:

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1 exp Patient Discharge/ (20028)
2 exp Aftercare/ or exp Convalescence/ (10216)
3 "Continuity of Patient Care"/ or exp "Recovery of Function"/ (49265)
4 ((patient* adj2 discharge*) or after?care or post medical discharge* or post?discharge* or convalescen*).ti,ab. (38163)
5 exp Stroke/ (90485)
6 exp brain ischemia/ or exp intracranial hemorrhages/ (132869)
7 (stroke or poststroke or tia or transient ischemic attack or ((cerebral vascular or cerebrovascular) adj (accident* or infarct*)) or CVA or cerebrovascular apoplexy or brain infarct* or (brain adj2 isch?emia) or (cerebral adj2 isch?emia) or (intracranial adj2 h?emorrhag*) or (brain adj2 h?emorrhag*)).ti,ab. (204881)
8 exp Heart Failure/ (92463)
9 (((cardia? or heart) adj (decompensation or failure or incompetence or insufficiency)) or cardiac stand still or ((coronary or myocardial) adj (failure or insufficiency))).ti,ab. (135313)
10 exp Pulmonary Disease, Chronic Obstructive/ (38585)
11 exp Emphysema/ (10912)
12 (copd or coad or chronic airflow obstruction* or (chronic adj2 bronchitis) or emphysema).ti,ab. (58516)
13 (chronic obstructive adj2 (lung* or pulmonary or airway* or airflow* or respiratory or bronchopulmonary) adj (disease* or disorder*)).ti,ab. (36565)
14 exp Pneumonia/ (76229)
15 (pneumoni* or peripneumoni* or pleuropneumoni* or lobitis or ((pulmon* or lung*) adj inflammation*)).ti,ab. (141791)
16 or/1-15 (781419)
17 exp Anti-Bacterial Agents/ (549766)
18 Antibiotic Prophylaxis/ (9748)
19 exp Macrolides/ (92986)
20 ((antibiotic* adj2 (prophylaxis or prophylactic or preemptive or pre-emptive)) or macrolide* or erythromycin or azithromycin or clarithromycin or azasite or azenil or azibiot or azin or azithrocin or azitromax or aztrin or hemomycin or misultina or sumamed or vinzam or zifin or zithromax or zitrocin or zitrotek or zmax).ti,ab. (51341)
21 or/17-20 (590273)
22 16 and 21 (38799)
23 Meta Analysis.pt. (50072)
24 Meta-Analysis/ or Meta-Analysis as Topic/ or exp Technology Assessment, Biomedical/ (72206)
25 (((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab. (183814)
26 (meta analy* or metaanaly* or health technolog* assess*).mp. (133214)
27 or/23-26 (263807)
28 22 and 27 (717)
29 limit 28 to (english language and yr="2009 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained] (282)
30 remove duplicates from 29 (262)

Appendix 1b: Literature Search Strategy for Addendum

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2014>, EBM Reviews - ACP Journal Club <1991 to June 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <June 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <2nd Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2014>, Embase <1980 to 2014 Week 28>, Ovid MEDLINE(R) <1946 to July Week 2 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 16, 2014>
Search Strategy:

1	exp Pulmonary Disease, Chronic Obstructive/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	38683
2	Chronic Obstructive Lung Disease/ use emez	70346
3	exp Emphysema/	42760
4	(copd or coad or chronic airflow obstruction* or (chronic adj2 bronchitis) or emphysema).ti,ab.	124284
5	(chronic obstructive adj2 (lung* or pulmonary or airway* or airflow* or respiratory or bronchopulmonary) adj (disease* or disorder*)).ti,ab.	76614
6	or/1-5	207582
7	exp azithromycin/	26824
8	exp Macrolides/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	93105
9	exp macrolide/ use emez	125894
10	Antibiotic Prophylaxis/	30758
11	((antibiotic* adj2 (prophylaxis or prophylactic or preemptive or pre-emptive)) or macrolide* or erythromycin or azithromycin or clarithromycin or azasite or azenil or azibiot or azin or azithrocin or azitromax or aztrin or hemomycin or misultina or sumamed or vinzam or zifin or zithromax or zitrocin or zitrotek or zmax).ti,ab.	106776
12	or/7-11	285604
13	(Meta Analysis or Controlled Clinical Trial).pt.	223587
14	Meta-Analysis/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or Meta-Analysis as Topic/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Technology Assessment, Biomedical/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	72466
15	Meta Analysis/ use emez or "Meta Analysis (Topic)"/ use emez or Biomedical Technology Assessment/ use emez	104349
16	(((systematic* or methodologic*) adj3 (review* or overview*)) or pooled analysis or published studies or published literature or hand search* or handsearch* or medline or pubmed or embase or cochrane or cinahl or data synthes* or data extraction* or HTA or HTAs or (technolog* adj (assessment* or overview* or appraisal*))).ti,ab.	372138
17	(meta analy* or metaanaly* or health technolog* assess*).mp.	260538
18	exp Randomized Controlled Trial/	724584
19	exp Random Allocation/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Double-Blind Method/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Control Groups/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed or exp Placebos/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed	349383
20	exp Randomization/ use emez or exp RANDOM SAMPLE/ use emez or Double Blind Procedure/ use emez or exp Triple Blind Procedure/ use emez or exp Control Group/ use emez or exp PLACEBO/ use emez	428335
21	(random* or RCT or RCTs or placebo* or sham* or (control* adj2 clinical trial*)).ti,ab.	2315015

22	or/13-21	3201712
23	6 and 12 and 22	1089
24	limit 23 to english language [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained]	985
25	limit 24 to yr="2013 -Current" [Limit not valid in DARE; records were retained]	111
26	remove duplicates from 25	96

Appendix 2: Evidence Quality Assessment for Rapid Review

Table A1: AMSTAR Scores of Systematic Reviews That Met the Inclusion Criteria

Author, Year	AMSTAR Score[a]	(1) Provided Study Design	(2) Duplicate Study Selection	(3) Broad Literature Search	(4) Considered Status of Publication	(5) Listed Excluded Studies	(6) Provided Characteristics of Studies	(7) Assessed Scientific Quality	(8) Considered Quality in Report	(9) Methods to Combine Appropriate	(10) Assessed Publication Bias	(11) Stated Conflict of Interest
Herath and Poole, 2013 (8)	10	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓
Yao et al, 2013 (9)	8	✓	✓		✓		✓	✓		✓	✓	✓
Donath et al, 2013 (10)	8	✓	✓	✓	✓		✓	✓		✓		✓
Simoens et al, 2013 (11)	7	✓		✓	✓		✓	✓		✓		✓

Abbreviation: AMSTAR, Assessment of Multiple Systematic Reviews.

[a]Maximum possible score is 11. Details of AMSTAR score are described in Shea et al. (6)

Table A2: GRADE Evidence Profile for RCTs Comparing Prophylactic AZM With Placebo in COPD

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Time to first exacerbation							
1 (RCT)	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (–1)[b]	Undetected	None	⊕⊕⊕ Moderate
Frequency of exacerbations							
1 (RCT)	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (–1)[b]	Undetected	None	⊕⊕⊕ Moderate
Duration of exacerbations							
1 (RCT)	Serious limitations (–1)[a]	No serious limitations	No serious limitations	Serious limitations (–1)[b]	Undetected	None	⊕⊕ Low
Gastrointestinal adverse effects							
2 (RCT)	Serious limitations (–1)[a]	Serious limitations (–1)[c]	No serious limitations	Serious limitations (–1)[d]	Undetected	None	⊕ Very low
Hearing impairment							
1 (RCT)	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (–1)[d]	Undetected	None	⊕⊕⊕ Moderate
Antibiotic resistance							
1 (RCT)	No serious limitations[a]	No serious limitations	No serious limitations	Serious limitations (–1)[d]	Undetected	None	⊕⊕⊕ Moderate

Abbreviations: AZM, azithromycin; COPD, chronic obstructive pulmonary disease; GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RCT, randomized controlled trial.
[a]For details on risk of bias, see Table A3.
[b]The following were not identified: minimal clinically important reduction in time to, rate of, or duration of exacerbations. Therefore, the relative clinical importance of these findings is poorly understood.
[c]Gastrointestinal adverse effects were scantily reported in both studies, with one finding a significant increase in the treatment arm (13) and the other finding no difference. (12)
[d]Adverse event results are poorly reported and are based on subgroup analysis and may lack adequate power to detect important differences (i.e., the Optimal Information Size criteria is not met).

Table A3: Risk of Bias Among RCTs Comparing Prophylactic AZM With Placebo in COPD

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Albert et al, 2011 (12)	No limitations	No limitations	No limitations	No limitations	No limitations
Mygind et al, 2010 (13)	Limitations[a]	No limitations	Limitations[b]	No limitations	No limitations

Abbreviations: AZM, azithromycin; COPD, chronic obstructive pulmonary disease; RCT, randomized controlled trial.
[a]Random sequence generation and allocation concealment were not well described, as only an abstract was available and attempts to contact authors were unsuccessful.
[b]Limited information on which to judge attrition bias; withdrawal rates were over 40%.
Note: Risk of bias assessment taken from Herath and Poole. (8)

Appendix 3: Evidence Quality Assessment for Addendum

Table A4: Risk of Bias Among RCTs Comparing Prophylactic AZM with Placebo in COPD, Published Between January 1, 2013 and July 17, 2014

Author, Year	Allocation Concealment	Blinding	Complete Accounting of Patients and Outcome Events	Selective Reporting Bias	Other Limitations
Uzun et al, 2014 (15)	No limitations[a]	No limitations[b]	No limitations[c]	No limitations[d]	No limitations
Berkhof et al, 2010 (16)	No limitations[e]	No limitations[b]	No limitations[f]	No limitations[d]	No limitations

Abbreviations: AZM, azithromycin; COPD, chronic obstructive pulmonary disease; RCT, randomized controlled trial.

[a]Adequate randomization and allocation concealment via computer allocation program with a 1:1 ratio and permutated block size of 10, stratified by use of low-dose long-term prednisolone. (15)

[b]Double-blind study, researchers and participants masked until completion of analysis.

[c]Intention-to-treat analysis was conducted on all randomized participants and also per protocol analysis (80% completion in placebo group, 87% in treatment group) for primary outcome.

[d]All pre-specified outcomes are reported.

[e]Adequate randomization and allocation concealment via computer allocation program with a 1:1 ratio and permutated block size of 4. (16)

[f]Primary and secondary analysis conducted using intention-to-treat principle (95% completion in placebo group, 90% in treatment group). (16)

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