Chaya Newfield

Mini CAT 1

Clinical Scenario:
60-year-old white female presents to the internal medicine department from ED with acute onset shortness of breath, dyspnea and productive cough. Symptoms began approximately 2 days before and had progressively worsened with no associated, aggravating, or relieving factors noted. She had similar symptoms approximately 1 year ago with an acute, chronic obstructive pulmonary disease (COPD) exacerbation requiring hospitalization. The patient wants to know if there is any medication she can take prophylactically to prevent further COPD exacerbations.

Search Question:

Is prophylactic antibiotic therapy with a macrolide safe and effective for reducing COPD exacerbations in elderly patients?

PICO search terms:

P	I	C	O
COPD	Macrolide	No treatment	Copd exacerbation
Geriatric patients	Antibiotic therapy	Placebo	morbidity
Elderly patients	Prophylactic antibiotics		Serious adverse events
Adults			
Chronic Obstructive Pulmonary Disease			

Search Strategy:

→ ideally I would look for the highest level of evidence, which is a systematic review or meta-analyses. If meta-analyses or systematic reviews were not available, I would look for randomized controlled trials. These studies examine the outcomes of two groups, one treated with the medication and one treated with placebo (or alternative medication) and then determine which one had the best outcomes. Of the RCTs, a double blinded study would be the highest level of evidence.
→ If RCTs were not available, I would look for a cohort study that would prospectively or retrospectively study a group of patients with COPD who were treated with prophylactic macrolide therapy to see their outcomes.

PubMed:

"Antibiotic prevention copd" → 95

Filter: 10 years→ 58

+macrolide → 24

Add "exacerbation" → 20

Google Scholar:

"Antibiotic prophylaxis copd" → 26,500

Filter: since 2017 → 9,920

+"exacerbation" → 4,050

Cochrane Database:

"copd" → 118

Filter: 2015 → 12

+"macrolide" → 3

I narrowed my articles by ruling out the ones that did not relate to my PICO question. For example, some articles discussed other classes of antibiotics besides macrolides, so I eliminated those. I specifically chose articles that looked at the outcome I focused on, exacerbations of COPD, in the adult or elderly population.

Article #1
Citation: Janjua S, Mathioudakis AG, Fortescue R, Walker RAE, Sharif S, Threapleton CJD, Dias S. Prophylactic antibiotics for adults with chronic obstructive pulmonary disease: a network meta-analysis. Cochrane Database of Systematic Reviews 2021, Issue 1. Art. No.: CD013198. DOI: 10.1002/14651858.CD013198.pub2. Accessed 16 March 2021.

Prophylactic antibiotics for adults with chronic obstructive pulmonary disease: a network meta-analysis

Sadia Janjua, Alexander G Mathioudakis, Rebecca Fortescue, Ruth AE Walker, Sahar Sharif, Christopher JD Threapleton, Sofia Dias

Link: https://www-cochranelibrary-com.york.ezproxy.cuny.edu/cdsr/doi/10.1002/14651858.CD013198.pub2/full?highlightAbstract=macrolid%7Ccopd%7Cmacrolide

Abstract:

Background

Chronic obstructive pulmonary disease (COPD) is a chronic respiratory condition characterised by persistent respiratory symptoms and airflow limitation. Acute exacerbations punctuate the natural history of COPD and are associated with increased morbidity and mortality and disease progression. Chronic airflow limitation is caused by a combination of small airways (bronchitis) and parenchymal destruction (emphysema), which can impact day-to-day activities and overall quality of life. In carefully selected patients with COPD, long-term, prophylactic use of antibiotics may reduce bacterial load, inflammation of the airways, and the frequency of exacerbations.

Objectives

To assess effects of different prophylactic antibiotics on exacerbations, quality of life, and serious adverse events in people with COPD in three separate network meta-analyses (NMAs), and to provide rankings of identified antibiotics.

Search methods

To identify eligible randomised controlled trials (RCTs), we searched the Cochrane Airways Group Specialised Register of trials and clinical trials registries. We conducted the most recent search on 22 January 2020.

Selection criteria

We included RCTs with a parallel design of at least 12 weeks' duration evaluating long-term administration of antibiotics prophylactically compared with other antibiotics, or placebo, for patients with COPD.

Data collection and analysis

This Cochrane Review collected and updated pair-wise data from two previous Cochrane Reviews. Searches were updated and additional studies included. We conducted three separate network meta-analyses (NMAs) within a Bayesian framework to assess three outcomes: exacerbations, quality of life, and serious adverse events. For quality of life, we collected data from St George's Respiratory Questionnaire (SGRQ). Using previously validated methods, we selected the simplest model that could adequately fit the data for every analysis. We used threshold analysis to indicate which results were robust to potential biases, taking into account each study’s contributions to the overall results and network structure. Probability ranking was performed for each antibiotic class for exacerbations, quality of life, and serious adverse events.

Main results

Characteristics of studies and participants

Eight trials were conducted at multiple sites that included hospital clinics or academic health centres. Seven were single-centre trials conducted in hospital clinics. Two trials did not report settings. Trials durations ranged from 12 to 52 weeks. Most participants had moderate to severe disease. Mean age ranged from 64 years to 73 years, and more males were recruited (51% to 100%). Forced expiratory volume in one second (FEV_1) ranged from 0.935 to 1.36 L. Most participants had previous exacerbations. Data from 12 studies were included in the NMAs (3405 participants; 16 treatment arms including placebo). Prophylactic antibiotics evaluated were macrolides (azithromycin and

erythromycin), tetracyclines (doxycyclines), quinolones (moxifloxacin) and macrolides plus tetracyclines (roxithromycin plus doxycycline).

Risk of bias and threshold analysis

Most studies were at low risk across domains, except detection bias, for which only seven studies were judged at low risk. In the threshold analysis for exacerbations, all comparisons in which one antibiotic was compared with another were robust to sampling variation, especially macrolide comparisons. Comparisons of classes with placebo were sensitive to potential bias, especially macrolide versus placebo, therefore, any bias in the comparison was likely to favour the active class, so any adjustment would bring the estimated relative effect closer to the null value, thus quinolone may become the best class to prevent exacerbations.

Exacerbations

Nine studies were included (2732 participants) in this NMA (exacerbations analyzed as time to first exacerbation or people with one or more exacerbations). Macrolides and quinolones reduced exacerbations. Macrolides had a greater effect in reducing exacerbations compared with placebo (macrolides: hazard ratio (HR) 0.67, 95% credible interval (CrI) 0.60 to 0.75; quinolones: HR 0.89, 95% CrI 0.75 to 1.04), resulting in 127 fewer people per 1000 experiencing exacerbations on macrolides. The difference in exacerbations between tetracyclines and placebo was uncertain (HR 1.29, 95% CrI 0.66 to 2.41). Macrolides ranked first (95% CrI first to second), with quinolones ranked second (95% CrI second to third). Tetracyclines ranked fourth, which was lower than placebo (ranked third). Contributing studies were considered as low risk of bias in a threshold analysis.

Quality of life (SGRQ)

Seven studies were included (2237 participants) in this NMA. SGRQ scores improved with macrolide treatment compared with placebo (fixed effect-fixed class effect: mean difference (MD) -2.30, 95% CrI -3.61 to -0.99), but the mean difference did not reach the minimally clinical important difference (MCID) of 4 points. Tetracyclines and quinolones did not improve quality of life any more than placebo, and we did not detect a difference between antibiotic classes.

Serious adverse events

Nine studies were included (3180 participants) in the NMA. Macrolides reduced the odds of a serious adverse event compared with placebo (fixed effect-fixed class effect: odds ratio (OR) 0.76, 95% CrI 0.62 to 0.93). There was probably little to no difference in the effect of quinolone compared with placebo or tetracycline plus macrolide compared with placebo. There was probably little to no difference in serious adverse events between quinolones or tetracycline plus macrolide. With macrolide treatment 49 fewer people per 1000 experienced a serious adverse event compared with those given placebo. Macrolides ranked first, followed by quinolones. Tetracycline did not rank better than placebo.

Drug resistance

Ten studies reported drug resistance. Results were not combined due to variation in outcome measures. All studies concluded that prophylactic antibiotic administration was associated with the development of antimicrobial resistance.

Authors' conclusions

This NMA evaluated the safety and efficacy of different antibiotics used prophylactically for COPD patients. Compared to placebo, prolonged administration of macrolides (ranked first) appeared beneficial in prolonging the time to next exacerbation, improving quality of life, and reducing serious adverse events. No clear benefits were associated with use of quinolones or tetracyclines. In addition, antibiotic resistance was a concern and could not be thoroughly assessed in this review. Given the trade-off between effectiveness, safety, and risk of antibiotic resistance, prophylactic administration of antibiotics may be best reserved for selected patients, such as those experiencing frequent exacerbations. However, none of the eligible studies excluded patients with previously isolated non-

tuberculous mycobacteria, which would contraindicate prophylactic administration of antibiotics, due to the risk of developing resistant non-tuberculous mycobacteria.

Article #2

Citation:
Pomares, Xavier, et al. "Clinical and safety outcomes of long-term azithromycin therapy in severe COPD beyond the first year of treatment." Chest 153.5 (2018): 1125-1133.
Clinical and Safety Outcomes of Long-Term Azithromycin Therapy in Severe COPD Beyond the First Year of Treatment
Xavier Pomares, MD; Concepción Montón, MD, PhD; Miriam Bullich, MD; Oscar Cuevas, PhD; Joan Carles Oliva, MStat; Miguel Gallego, MD, PhD; and Eduard Monsó, MD, PhD
LINK: https://www.sciencedirect.com/science/article/abs/pii/S0012369218302459

Abstract:
Background
Exacerbations of COPD (ECOPD) are a major cause of mortality and morbidity. Continuous cyclic azithromycin (CC-A) reduces the exacerbation rate, but it is unknown whether it remains effective and safe beyond the first year.
Methods
This study was a retrospective analysis of patients with severe COPD (Global Initiative for Chronic Obstructive Lung Disease grade D) with ≥ 4 moderate to severe ECOPD who received CC-A (500 mg three times per week) as add-on therapy. Patients treated over 24 months were considered long-term continuous cyclic azithromycin (LT-CC-A) users, and ECOPD, hospitalizations, and length of hospital stays during the first, second, and third years were compared with the previous 12 months. Microbiologic monitoring, assessment of macrolide resistance, and analysis of side effects were maintained throughout the study period.
Results
A total of 109 patients with severe COPD treated with CC-A (39 for ≥ 24 months) comprised the LT-CC-A group (35.8%). This group presented average reductions in ECOPD from baseline of 56.2% at 12 months, 70% at 24 months, and 41% at 36 months, paralleled by respective reductions in hospitalizations of 62.6%, 75.8%, and 39.8%. ECOPD due to common microorganisms fell by 12.5% and 17.3% at 12 and 24 months of LT-CC-A, respectively, with a 50% increase in macrolide resistance. Pseudomonas aeruginosa ECOPD rose by 7.2% and 13.1% at these two time points. CC-A therapy was well tolerated with few side effects: digestive disorders in the short term (7.1%) and hearing loss in the long term (5.1%).
Conclusions
LT-CC-A therapy over a 24- to 36-month period in patients with COPD (Global Initiative for Chronic Obstructive Lung Disease grade D) achieved sustained reductions in ECOPD and hospitalizations of > 50% with few adverse events, although macrolide resistance increased.

Article #3

Citation:
Cao, Yueqin, et al. "Effects of long-term macrolide therapy at low doses in stable COPD." International journal of chronic obstructive pulmonary disease 14 (2019): 1289.

Effects of long-term macrolide therapy at low doses in stable COPD
Yueqin Cao,1,2 Shurui Xuan,1 Yunhui Wu,1 and Xin Yao1
LINK: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6572718/

Abstract:
Background: Chronic obstructive pulmonary disease (COPD) is currently the fourth largest fatal disease in the world, and is expected to rise to third place by 2020. Frequent acute exacerbations lead to increased mortality. Some suggestions for prophylactic use of macrolides in preventing COPD exacerbations have been raised, but there are still several issues that need to be addressed, such as target population, the course of treatment, therapeutic dose, and so on.
Objective: To evaluate, via exploratory meta-analysis, the efficacy of long-term macrolide therapy at low doses in stable COPD.
Methods: A systematic literature search was performed in PubMed, Embase, and Cochrane database from inception to March 28, 2019. Randomized controlled trials (RCT) which reported long-term use of macrolides in prevention of COPD were eligible.
Results: A total of 10 articles were included in this study. It was found that there was a 23% relative risk reduction in COPD exacerbations among patients taking macrolides compared to placebo ($P<0.01$). The median time to first exacerbation was effectively prolonged among patients taking macrolides vs placebo ($P<0.01$). Sub-group analysis showed erythromycin was advantageous and older patients were less responsive to macrolides.
Conclusions: Long-term low dose usage of macrolides could significantly reduce the frequency of the acute exacerbation of COPD. The treatment was well tolerated, with few adverse reactions, but it was not suitable for the elderly. It is recommended that this treatment regimen could be used in patients with GOLD grading C or D, because they have a higher risk of acute exacerbation and mortality. It needs to be further discussed whether this treatment should last for 12 months or longer.

Article #4

Donath, Elie, et al. "A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with Chronic Obstructive Pulmonary Disease." Respiratory medicine 107.9 (2013): 1385-1392.

A meta-analysis on the prophylactic use of macrolide antibiotics for the prevention of disease exacerbations in patients with Chronic Obstructive Pulmonary Disease

Elie Donath a, *, Abubakr Chaudhry b , Leonel F. Hernandez-Aya c , Louis Lit d

https://www.sciencedirect.com/science/article/pii/S0954611113001765

Abstract:

Introduction
Macrolides are of unique interest in preventing COPD exacerbations because they possess a variety of antibacterial, antiviral and anti-inflammatory properties. Recent research has generated renewed interest in prophylactic macrolides to reduce the risk of COPD exacerbations. Little is known about how well these recent findings fit within the context of previous research on this subject. The purpose of this article is to evaluate, via exploratory meta-analysis, whether the overall consensus favors prophylactic macrolides for prevention of COPD exacerbations.
Methods
EMBASE, Cochrane and Medline databases were searched for all relevant randomized controlled trials (RCTs). Six RCTs were identified. The primary endpoint was incidence of COPD exacerbations. Secondary endpoints including mortality, hospitalization rates, adverse events and likelihood of having at least one COPD exacerbation were also examined.
Results
There was a 37% relative risk reduction (RR = 0.63, 95% CI: 0.45–0.87, p value = 0.005) in COPD exacerbations among patients taking macrolides compared to placebo. Furthermore, there was a 21% reduced risk of hospitalization (RR = 0.79, 95% CI: 0.69–0.90, p-value = 0.01) and 68% reduced risk of having at least one COPD exacerbation (RR = 0.34, 95% CI 0.21–0.54, p-value = 0.001) among patients taking macrolides versus placebo. There was also a trend toward decreased mortality and increased adverse events among patients taking macrolides but these were not statistically significant.
Conclusions
Prophylactic macrolides are an effective approach for reducing incident COPD exacerbations. There were several limitations to this study including a lack of consistent adverse event reporting and some degree of clinical and statistical heterogeneity between studies.

Author (Date)	Level of Evidence	Sample/ Setting	Outcomes studied	Key Findings	Limitations and Biases
Sadia Janjua, Alexander G Mathioudakis, Rebecca Fortescue, Ruth AE Walker, Sahar Sharif, Christopher JD Threapleton, Sofia Dias	Network Meta-analysis	Eight trials were conducted at multiple sites including hospital clinics and academic health centers. Mean age of patients were 64-73 years.	Effects of different prophylactic antibiotics on exacerbations, quality of life, and serious adverse events and drug resistance in people with COPD	Macrolides were better in reducing exacerbations compared to control treatment. There was no clear difference in exacerbations when quinolone or tetracycline	None of the studies in this review excluded patients with previously isolated non-tuberculous mycobacteria, which would contraindicate prophylactic

(2021)		Data from 12 studies were included (3405 participants) Seven trials were single-center trials in hospital clinics. Two did not report settings.		was compared with a control treatment. Tetracyclines were ranked lower than placebo in reducing exacerbations. Macrolides improved quality of life compared with control treatment. Macrolides were more effective in reducing serious unwanted events. There was no clear benefit for serious unwanted events with quinolone, tetracycline, or combined macrolide plus tetracycline compared with control treatment. All studies concluded that prophylactic antibiotic administration was associated with the development of	administration of antibiotics (because they can increase the risk of developing resistant non-tuberculous mycobacteria.) In some studies, the people collecting the information knew which patients were included in which treatment group, and also knew the patient results when treatments were completed. However, because of the large same size, the results were unlikely to be influenced by this.

				antimicrobial resistance.	
Xavier Pomares, MD; Concepción Montón, MD, PhD; Miriam Bullich, MD; Oscar Cuevas, PhD; Joan Carles Oliva, MStat; Miguel Gallego, MD, PhD; and Eduard Monsó, MD, PhD (2018)	Retrospective Cohort	The study focused on patients with severe COPD (Global Initiative for Chronic Obstructive Lung Disease grade D) with greater than 4 moderate to severe ECOPD who received CC-A (500 mg three times per week) as add-on therapy. 109 patients with severe COPD and more than 4 ECOPD in the previous year from the cohort of 505 patients controlled at the Respiratory Day Care Unit were eligible for CC-A therapy and agreed to participate in	effectiveness and safety of LT-CC-A therapy over a 24-month period in patients with severe COPD who had frequent exacerbations.	CC-A therapy was well tolerated over the 24- and 36-month periods, with few side effects. Attempts to withdraw the treatment in patients who had attained a low frequency of exacerbations following its initiation did not succeed in approximately one-half of the cases, a finding that confirms the long-term benefits of CC-A treatment in patients with COPD exacerbations. An increase in macrolide resistance was observed in common potential pathogenic microorganisms recovered	The main limitation of this study was the fact that it is an observational study without a control group. It also does not cover the long-term effects of CC-A therapy on macrolide resistance in the community. In addition, in regards to negative side effects, no standard audiometry was performed during patient follow up (patients were asked about hearing loss, but not tested.)

		the study. The ST-CC-A group comprised 70 of the 109 participants (64.2%).		during follow-up. LT-CC-A therapy over a 24- to 36-month period in patients with COPD (Global Initiative for Chronic Obstructive Lung Disease grade D) achieved sustained reductions in ECOPD and hospitalizations of > 50% with few adverse events, although macrolide resistance increased.	
Yueqin Cao,1,2 Shurui Xuan,1 Yunhui Wu,1 and Xin Yao1 (2019)	meta-analysis	Ten articles were retained in this study after manual curation. All the patients were in stable phase and had a history of acute exacerbations before enrollment. A total of 1,521 patients were randomly allocated to the	Effects of prophylactic macrolide therapy for patients with stable COPD, specifically in regards to reduction of frequency of acute exacerbations of COPD, side effects, and antibiotic resistance.	Nine studies involving 1,508 participants reported the rate of exacerbations per patient per year, showing a reduction in the rate of exacerbations in the macrolides group (SMD=−2.55, 95% CI=−3.54–−1.57, P<0.01, I2=97%;	In the literature included, the sample size of some is small, which reduces the efficiency of statistical analysis. In order to obtain more comprehensive and objective conclusions on the efficacy of

		macrolides treatment group, and 1,418 were randomly allocated to the control group. The study duration lasted from 3 months to 12 months.		Nine papers studied the adverse effects, showing that the incidence of gastrointestinal reaction was 5.68% (52/916) in the treatment group and 4.90% (45/919) in the control group. The difference was not statistically significant (P>0.25).	macrolide antibiotics in the treatment of stable COPD, more randomized, doubleblind controlled trials with a dedicated design, reliable methods, and high quality are needed.
Elie Donath, Abubakr Chaudhry, Leonel F. Hernandez-Aya, Louis Lit (2013)	meta-analysis	six studies, with a total of 1677 patients, were selected for inclusion in the meta-analysis. An additional two cohort studies were also noted, but not included as part of the overall meta-analysis. They generally included patients among the ages of 65-75. They were mostly evaluating patients with severe to very	The primary endpoint studied was total number of exacerbations as a function of person-years. Secondary endpoints included mortality risk, hospitalization risk, likelihood of having at least one COPD exacerbation, and adverse events.	: There was a 37% relative risk reduction (RR Z 0.63, 95% CI: 0.45e0.87, p value Z 0.005) in COPD exacerbations among patients taking macrolides compared to placebo. Furthermore, there was a 21% reduced risk of hospitalization (RR Z 0.79, 95% CI: 0.69e0.90, pvalue Z 0.01) and 68% reduced risk of having at least one COPD exacerbation	The findings from one of the six studies included was highly inconsistent with the rest, which may have been due to the limited length of the study and the small number of total exacerbations observed. In general, there was some degree of clinical heterogeneity between teh studies because they were conducted in

		severe COPD with baseline FEV1% values ranging from 20% to 50%. Studies lasted for 3-12 months.		(RR Z 0.34, 95% CI 0.21e0.54, p-value Z 0.001) among patients taking macrolides versus placebo.	different countries, had different grading criteria for COPD severity and each used different macrolides with various dosing regiments. There was also variation in study lengths and adverse events were inconsistently reported between studies. l as support the overall conclusions from this meta-analysis. Lastly, prophylactic macrolides have become increasingly well established as an important treatment consideration in non-cystic fibrosis bronchiectasis and there were no screening programs in place among these studies to

					identify patients with underlying bronchiectasis

Conclusion(s):
Article #1: Janjua et al concluded that exacerbations were reduced, quality of life was improved, and unwanted events were fewer with macrolides compared with control treatment. Macrolides reduced the odds of a serious adverse event compared with placebo (fixed effect-fixed class effect: odds ratio (OR) 0.76, 95% CrI 0.62 to 0.93). However, prophylactic antibiotic administration was associated with the development of antimicrobial resistance. Given the trade-off between effectiveness, safety, and risk of antibiotic resistance, prophylactic administration of antibiotics may be best reserved for selected patients, such as those experiencing frequent exacerbations.
Article #2: Pomares, Xavier, et al. concluded that Continuous cyclic azithromycin (CC-A) therapy over a 24- to 36-month period in patients with COPD (Global Initiative for Chronic Obstructive Lung Disease grade D) achieved sustained reductions in exacerbations of COPD and hospitalizations of > 50% with few adverse events, although macrolide resistance increased.
Article #3: Long-term low dose usage of macrolides could significantly reduce the frequency of the acute exacerbation of COPD. The treatment was well tolerated, with few adverse reactions, but it was not suitable for the elderly. It is recommended that this treatment regimen could be used in patients with GOLD grading C or D, because they have a higher risk of acute exacerbation and mortality. It needs to be further discussed whether this treatment should last for 12 months or longer.
Article #4: prophylactic macrolides seem to have a positive net effect among individuals with more severe forms of COPD. This benefit seemed to extend to all outcomes that were assessed e in particular, the incidence of COPD exacerbations, the hospitalization rate and likelihood of having at least one COPD exacerbation all suggested highly statistically significant benefit favoring the use of macrolides versus placebo.

Clinical Bottom Line:
The clinical bottom line is that macrolides such as azithromycin may be effective in reducing exacerbations of COPD in the adult population. The articles did highlight that certain precautions must be taken, such as being aware of antibiotic resistance, different treatment options/precautions for the elderly population, and potential side effects, most notably GI disturbances. Many of the articles also noted that this treatment may be restricted to patients with COPD who have a history of frequent exacerbations, instead of the general population with COPD, due to the benefit to risk ratio. In summary, for those with frequent exacerbations of COPD, continuous prophylactic administration of a macrolide may reduce the exacerbations and help improve the patients' quality of life.

Weight of Evidence:
Article 1: This article is a Cochrane review that was published this year. It has evidence based on 12 studied with large sample sizes. It is based on RCTs with a parallel design of at least 12 weeks' duration evaluating long-term administration of antibiotics prophylactically compared with other antibiotics, or placebo, for patients with COPD. In the article's quality of evidence analysis, it noted "We did not find any concerns about the ways in which studies were carried out, except that for some studies, people collecting the information knew (1) which patient was included in which treatment group, and (2) patient results when treatments were completed. Overall, the numerical information was robust and was unlikely to be influenced by differences noted between individual studies."
Article 3 This article is a meta-analysis that was conducted in 2019, making it both recent and based on the highest level of research. It is based on 10 articles with an overall total of 1,521 people in the intervention group and 1,418 people in the control group. This large sample size adds to the weight of the evidence. It is not placed the highest on my list because it noted that some of the individual studies used in this article contain relatively small sample sizes.
Article 2: This retrospective cohort was conducted in 2018, and included over 100 participants in the study. I weighed this article higher than Article 4 because it is more recent. I also think this article added a lot of value because it specifically studies the effectiveness and safety of macrolide therapy beyond the first year of treatment. This study followed the patients in the treatment cohort for 24-36 months.
Article 4: This article has a high level of research, being a meta-analysis, but it is at the bottom of the list because it was published in 2013. It is also based on only 6 RCTs, which is less than the number of articles studied in the other meta-analyses that I included. I do appreciate how clearly the article stated the primary and secondary endpoints, and also detailed the limitations of the study and what was done to counter them.

Magnitude of any effects:
All of the articles noted above all came to the same conclusion that long term prophylactic macrolide therapy does help in decreasing COPD exacerbations. One article noted that the risks do not outweigh the benefits in the elderly population, which the other articles did not mention. Because of the potential for antibiotic resistance, the articles all indicated that this treatment should only be considered in patients who are prone to frequent exacerbations. I would consider the magnitude of the combined results of these articles to be substantial in favor of macrolide therapy.

Clinical Significance:
The clinical bottom line that I have derived from these articles is that patients who are prone to COPD exacerbations should be treated with macrolide therapy prophylaxis. If providers are debating between macrolides and other classes of antibiotics, macrolides are studied to be more effective at reducing adverse events.

Other considerations:
More studies are needed to specifically look at the benefit to risk ratio in the elderly population. In addition, more research on the increase in antibiotic resistance due to long term macrolide treatment are necessary. Further studies should also make sure to excluded patients with previously isolated non-tuberculous mycobacteria, because that condition would contraindicate prophylactic administration of antibiotics.