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Effects of Antibiotics on Exacerbations for Patients with Chronic Obstructive Pulmonary Disease (COPD)

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ABSTRACT

The use of antibiotics for treating exacerbations in patients with chronic obstructive pulmonary disease (COPD) has been a topic of controversy since first studied in the 1950s and 1960s. This paper analyzes the effects of a course of antibiotics on time until next exacerbation in patients with COPD. Five recent randomized control trials were examined. The antibiotic most often studied was azithromycin, a macrolide. Azithromycin decreased the length of time to first exacerbation compared to placebo in three studies; two other studies depicted sub analyses to support azithromycin as superior to placebo. Overall, antibiotics decreased the length of time between exacerbations, especially azithromycin. Treating exacerbations with antibiotics was more effective in certain patient populations such as patients of older age, a smoking history, or a milder form of COPD. It is important for these patients to be screened appropriately with continuous follow-up when administering azithromycin to decrease exacerbations in patients with COPD.

BACKGROUND

The World Health Organization projects chronic obstructive pulmonary disease (COPD) to be the 3rd leading cause of death by 2030.[1] COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.[2] It has deleterious health effects that accumulate over the lifespan, typically manifest in older age and are common among smokers.

Prevalence

The prevalence of COPD in the United States varies from <4% in Hawaii, Colorado, and Utah to >9% in Alabama, Tennessee, Kentucky, and West Virginia. States with the highest COPD prevalence are clustered along the Ohio and lower Mississippi Rivers.[3] Worldwide prevalence and

mortality rates of COPD are grimmer and are expected to place great strain on worldwide health care systems in the coming decades.

Pathophysiology

COPD is a culmination of the effects of the inflammatory response system which damages the airways resulting in airway limitation, obstruction and/or loss of elastic recoil. Triggers activate neutrophils and macrophages in the inflammatory response system, which release proteases that cause tissue destruction and promote hypersecretion of the airways. When the destruction happens at the level of the alveoli, there is a loss of elastic recoil and surface area resulting in a decrease of oxygen exchange. All these factors can result in pulmonary hypertension, respiratory infections, and other comorbidities.[4]

Diagnosis of the disease is obtained by assessing patient symptoms, evaluating risk factors and pulmonary function testing. The classic signs of a patient with COPD are frequent respiratory exacerbations, a barrel shaped chest, and hyperinflation of the lungs.[4] The Anthonisen Criteria defines an exacerbation as an increase of symptoms that a patient with COPD experiences because of their condition. Symptoms include an increase in sputum production, sputum volume, dyspnea and cough. [5] Exacerbations can lead to increased susceptibility to infections, an increase in hospitalizations and a decrease in quality of life.

Standards of Care and Treatment

The current standard treatment regimen for COPD in the 2018 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report involves a long or short acting antimuscarinic/anticholinergic inhaler and in some cases concurrent corticosteroids. Antibiotics are part of a later course of treatment that includes azithromycin given 250mg per day or 500mg given three times per week or erythromycin given 500mg twice per day for one year in patients

prone to exacerbations. This regimen of antibiotics, compared to usual care, has been shown to reduce the risk of exacerbations compared to usual care. However, no data are available showing the efficacy or safety of chronic azithromycin treatment to prevent COPD exacerbations beyond one year of treatment.[6] The use of azithromycin as part of the COPD treatment regimen is continuously being reviewed because of concerns about antibiotic resistance, adverse effects of impaired hearing, and development of cardiac abnormalities such as prolonged QT interval.[7]

Antibiotic Stewardship

Finding the balance between the benefits of antibiotic therapy to individual patients and the potential harms to both patients and society created by antibiotic overuse resulting in microbial resistance is especially relevant to COPD patients. These patients are at higher risk for infections and exacerbations, which have major negative health outcomes. COPD exacerbations are considered multifactorial; evidence suggests that bacterial infections are their primary cause.[8,9] As such, COPD exacerbations are frequently controlled with antibiotics. To decrease the risk of drug resistant bacteria antibiotics should be used wisely. The inappropriate use of antibiotics, both overuse and misuse, is considered a major public health concern. Antibiotic stewardship is a coordinated program that involves a collaborative effort to educate prescribers about the correct ways to administer antibiotics to reduce the risk of drug resistance bacteria and the spread of those resistant strains.[10]

Other research

Other diagnostic and treatment modalities to reduce exacerbations may be better than initiating antibiotic therapy empirically. Although bacterial infections are the most likely cause of exacerbations, confirmation of this hypothesis by measurements of the bacterial loads in the airways is limited. Analysis of sputum and swab cultures are unremarkable. Measuring

procalcitonin levels to assess for pulmonary infection as the cause of exacerbations was explored.[11] This investigation found these levels to be accurate for diagnosing infection; however, the quality of the available evidence was low to moderate. Another study examined non-invasive ventilation in ICU patients, instead of oral antibiotics, for decreasing the duration and frequency of exacerbations.[12] Although non-invasive ventilation was found to be superior to antibiotics, the findings were limited to hospitalized patients.

Existing Research

A systemic review by the Cochrane Library published in 2013 analyzed whether regular treatment of COPD patients with antibiotics reduced exacerbations. Seven randomized controlled trials investigated azithromycin, erythromycin, clarithromycin, and moxifloxacin. On average, the participants were 66 years old and had either moderate or severe COPD. The results showed that the use of continuous antibiotics, especially with a macrolide, resulted in a clinically significant benefit for reducing exacerbations and lengthening the time to first exacerbation in patients with COPD.[13]

This paper examines the effect of antibiotic therapy compared to no antibiotic therapy on length to first exacerbation in patients diagnosed with COPD (stages 1-4). The 2018 GOLD guidelines mention treatment with macrolide antibiotics but warn of adverse effects, such as of impaired hearing and cardiovascular abnormalities, in particular, QT interval prolongation. In view of potential serious adverse effects, determining whether antibiotics should be continued as part of standard treatment is relevant to practice. This paper builds upon the 2013 Cochrane review which found that the continuous use of antibiotics up to one year, especially azithromycin, resulted in a clinically significant benefit of reducing COPD exacerbations. Since Cochrane's review was conducted in 2013, more recent investigations are explored in this paper. While the long-term use of antibiotics remains controversial because there are no studies which measure their use past one

year,[14] the role of antibiotics for reducing COPD exacerbations may still be beneficial for decreasing patient morbidity and burdens on the health care system.

DISCUSSION

Literature search

The literature search accessed several databases including PubMed, Science Direct, Cochrane Library, Trip, and International Journal of COPD. The search terms used were chronic obstructive pulmonary disease/COPD AND antibiotics/azithromycin/macrolide/doxycycline AND exacerbations/relapse/recurrence. Articles were screened by title and abstract. Articles were excluded if they did not address the topic question with specific analysis on time to first/next exacerbation and frequency of exacerbations. For those studies that were not excluded, a full text of the article was obtained, and further exclusion was made based on content. The reference lists were screened and cross referenced for relevant articles and systemic reviews to ensure thoroughness of the review. A step-by-step critique of each article was performed to check for quality and validity. Most of the articles that were chosen were published within the last 5 years and contained most of their cited references within the last 5 years.

Summary of Evidence

Five randomized controlled trials were included in this review. Four studies were published between 2013 and 2018 with one article published in 2011. Three studies measured time to first exacerbation with azithromycin compared to placebo,[15-17] while another study compared doxycycline to placebo.[18] The fifth study reviewed a regimen of three different antibiotics (moxifloxacin, doxycycline, and azithromycin) to obtain results in a sub analysis on time to first exacerbation and frequency of exacerbations.[19] Azithromycin is a macrolide, doxycycline is a tetracycline, and moxifloxacin is a fourth-generation fluoroquinolone. The study durations varied

from three months to two years and all used intention-to-treat analysis. The focus for this review was time to next exacerbation (TTNE).

Four out of the five studies quantified TTNE. The study by Albert et al determined that the median TTNE with azithromycin was 266 days compared to 174 days with placebo.[15] Han et al showed a median time of 377 days with azithromycin plus steroid and 110 days with steroid only.[16] Uzun et al determined a median time of 130 days with azithromycin and 59 days with placebo.[17] All three studies showed a reduction in TTNE for a length of one year with azithromycin compared to without it. These findings are consistent with those found in the 2013 Cochrane review.

A study by Velzen et al compared a 7-day course of doxycycline to placebo and found no statistical difference in TTNE.[18] The median TTNE for the doxycycline and placebo groups were 148 days and 161 days respectively.

A study performed by Brill et al did not specifically quantify TTNE but rather in a sub analysis quantified the frequency of exacerbations between different antibiotics (moxifloxacin, doxycycline, and azithromycin) and placebo when taken for a period of 13 weeks. According to this study, the exacerbations in the doxycycline group increased compared to placebo, whereas in the azithromycin group they were statistically comparable to placebo. Azithromycin showed the least frequency of exacerbations at 0.83 and doxycycline had the highest frequency of 2.05. [19] These findings are consistent with the results for azithromycin found in studies by Albert et al and Uzun et al. Albert et al found that azithromycin reduced exacerbations to a frequency of 1.48 compared to placebo's frequency of 1.83, a rate ratio of 0.83.[15] Uzun et al also showed a frequency reduction of exacerbations, 1.32 for azithromycin and 3.22 for placebo; a rate ratio of 0.6.[16] No statistically significant decrease of exacerbations was found with doxycycline by Velzen et al.[15-18]

These results continue to confirm azithromycin as the better antibiotic for decreasing exacerbations in COPD patients.

The studies' findings are summarized in Table 1. A summary of rate ratios and P values is listed in Table 2.

Study	Outcome	No. participants	Dosing regimen	Antibiotic Group results	Placebo Group Results	P value
Albert 2011	Time to first exacerbation	1,142	Azithromycin 250mg/day x1 year or placebo	266 days	174 days	P<0.001
Han 2014	Time to first exacerbation	1,113	Azithromycin 250m/day x1 year or placebo	377 days	110 days	P=0.0002
Uzun 2014	Time to first exacerbation (secondary)	92	Azithromycin 500mg 3x per week x1 year or placebo	130 days	59 days	P=0.001
Velzen 2017	Time to next exacerbation	305	Doxycycline 100mg (200mg on day 1) x7days or placebo	148 days	161 days	P=0.91
Brill 2015	Sub analyses of frequency of exacerbation	99	Moxifloxacin 400m/day for 5 days every 4weeks OR Doxycycline 100mg/day for 13wks OR Azithromycin 250mg 3x per week for 13weeks or placebo	Moxifloxacin 1.36, Doxycycline 2.05, Azithromycin 0.83	Baseline rate	Moxifloxacin P=0.44, Doxycycline P=0.06, Azithromycin P=0.66

Table 1. Characteristics of Studies Reviewed.

Study	Rate ratio	P value
Brill 2015	Moxifloxacin 1.36, Doxycycline 2.05, Azithromycin 0.83	Moxifloxacin P=0.44, Doxycycline P=0.06, Azithromycin P=0.66
Uzun 2014	Azithromycin 0.6	P=0.003
Albert 2011	Azithromycin 0.83	P=0.008

Table 2. Frequency of exacerbations.

Study interventions and patient parameters

All five studies had patients with a median age ranging from 64 to 70 years old, a history of smoking, and a clinical diagnosis of COPD.[17-19] Albert et al and Han et al included patients on continuous oxygen.[15,16] Three studies used an antibiotic for a total of one year. The other two

studies used shorter courses of seven days or 13 weeks. All study parameters were analyzed using a hazard ratio analysis. Han et al specifically looked at patient characteristics that predicted benefit from antibiotic therapy of exacerbations. The parameters which favored the benefits of azithromycin were age >65, former smoking status, and diagnosis of mild COPD at GOLD stage 2.[16] Albert et al found that the same patient parameters were associated with benefits from azithromycin therapy.[15] Velzen et al described a different outcome of patient parameters favoring doxycycline with age <65, no difference with smoking status, and slight favor for moderate form of COPD GOLD stage 3.[18] This evidence suggests that azithromycin reduces exacerbations, especially in patients that are >65 years old, are former smokers, and have a milder GOLD stage of COPD. See Appendix for figures on patient parameters and hazard ratios.

These studies were limited because they lacked a comparison with a placebo, whereas Brill et al did find statistically significant benefits of antibiotics compared to placebo. Furthermore, none of the studies examined the use of antibiotics for over a year. Nonetheless, the studies did have results that were statistically significant for the comparisons that were made.[13]

CONCLUSION

The evidence about antibiotic use for COPD exacerbations that was presented in the 2013 Cochrane Review is updated by this paper. Current evidence suggests that azithromycin is effective for decreasing TTNE and that patients experiencing an increase in exacerbations may benefit from adding azithromycin to the usual treatment regimen. Furthermore, specific subgroups of patients are likely to benefit more than others, including patients older than age 65, former smokers, and patients with a milder form of COPD. Factors that must be considered before administering antibiotics for COPD exacerbations are patient age, smoking status and history, severity of COPD, other comorbidities, and the risk versus benefits of using antibiotics in general.

Continuous and regular follow-up for monitoring these patients is recommended while they are on antibiotics for COPD exacerbations.

Evidence supporting the benefits of azithromycin over its adverse effects of impaired hearing and cardiac abnormalities is limited. Researchers suggest including a baseline ECG and hearing test as part of medication pre-administration.[20] When azithromycin is not a treatment option for patients, other antibiotics that may be used include dirithromycin, ofloxacin, ciprofloxacin and trimethoprim-sulfamethoxazole.[21]

Future research

Additional studies are recommended to address gaps in knowledge such as studies comparing antibiotic regimens for greater than one year, comparing different regimens of azithromycin, directly comparing other classes of antibiotics to azithromycin, examining the effects of different antibiotic classes on the specific subset of patients mentioned, and specifically screening for side effects such as cardiac abnormalities and hearing deficits.

Current studies are underway to determine whether the benefits of treatment of COPD exacerbations with antibiotics outweigh the risks of antimicrobial resistance and side effects. The results of the ABACOPD study by BioMed Central Pulmonary Medicine are expected soon. This sufficiently powered double-blind placebo-controlled trial evaluates whether antibiotics, known to increase antibiotic resistance, are really needed in a well-defined patient cohort receiving state of the art treatment in all other aspects including systemic corticosteroids.[22] Another study called The Belgian Trial by the International Journal of COPD should be released soon. It is a randomized, double-blinded, placebo-controlled trial that investigates whether azithromycin might be effective and safe when initiated at the onset of a severe exacerbation for a limited duration and at a low dose. Its purpose is to establish a more appropriately restricted use of azithromycin so that the benefits counterbalance potential side effects.[23]

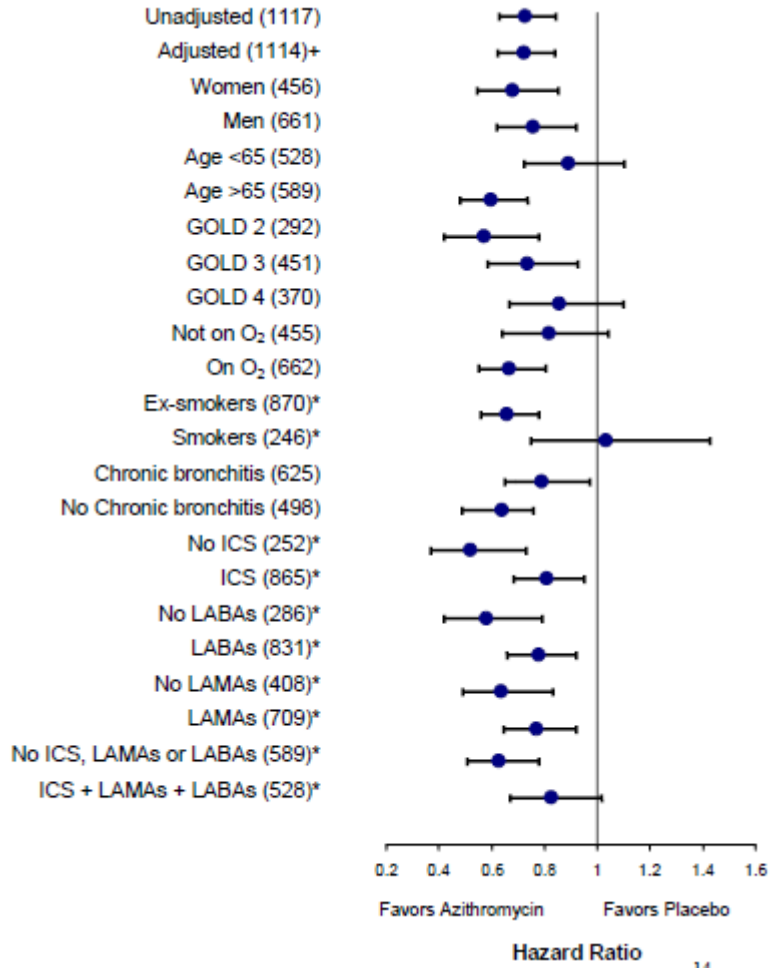
APPENDIX

Section I

Subgroup (n)	HR	95% CI for HR	*P* Value*	*P* Value for Interaction
All (1,113)	0.71	0.61–0.83	<0.0001	
Women (455)	0.69	0·55–0.87	0.001	0.75
Men (658)	0.72	0.59–0.89	0.002	
GOLD II (292)	0.55	0.40–0.75	0.0002	0.04
GOLD III (451)	0.71	0.56–0.90	0.004	
GOLD IV (370)	0.84	0.65–1.08	0.18	
Ex-smoker (867)	0.65	0.55–0.77	<0.0001	0.03
Smoker (246)	0.99	0.71–1.38	0.95	
Chronic bronchitis symptoms present (526)	0.76	0.62–0.94	0.01	0.25
Chronic bronchitis symptoms absent (581)	0.64	0.52–0.80	0.0001	
No ICS, LAMA, LABA (100)	0.42	0.23–0.77	0.005	0.29
ICS only (57)	0.65	0.31–1.38	0.26	
LAMA only (77)	0.60	0.33–1.11	0.10	
LABA only (21)	0.42	0.15–1.18	0.10	
ICS and LAMA (51)	1.19	0.63–2.23	0.59	
ICS and LABA (229)	0.74	0.52–1.05	0.09	
LAMA and LABA (53)	0.47	0.23–0.98	0.04	
ICS, LAMA, and LABA (525)	0.76	0.62–0.94	0.01	
No long-term oxygen use (454)	0.80	0.62–1.03	0.08	0.23
Long-term oxygen use (659)	0.66	0.55–0.80	<0.0001	
Age ≤ 65 (571)	0.84	0.68–1.04	0.1101	0.02
Age > 65 (542)	0.59	0.47–0.74	<0.0001	

Definition of abbreviations: CI = confidence interval; GOLD = Global Initiative for Chronic Obstructive Lung Disease; HR = hazard ratio; ICS = inhaled corticosteroids; LABA = long-acting β-agonists; LAMA = long-acting muscarinic agents.
All models included age, sex, clinic, smoking status at baseline, FEV_1% predicted at baseline, concomitant medications for COPD, and oxygen use except GOLD status models that used GOLD category instead of FEV_1%.

Figure 1. Han 2014 hazard ratio for exacerbations patient subgroup analyses.[16]
Excerpted from Han MK, Tayob N, Murray S, Dransfield MT, Washko G, Scanlon PD, et al. Predictors of chronic obstructive pulmonary disease exacerbation reduction in response to daily azithromycin therapy. *American Journal of Respiratory and Critical Care Medicine*. 2014;189(12):1503-1508. doi: 10.1164/rccm.201402-0207OC.



Interaction	P value	Description
Azithromycin * age (< 65 vs ≥ 65)	P = 0.012	Older = more effect
Azithromycin * COPD Hospitalizations	P = 0.053	Hospitalization = less effect
Azithromycin * Gender	P = 0.550	
Azithromycin * Smoking at enrollment	P = 0.012	Smokers = less effect
Azithromycin * FEV1 (% pred)	P = 0.234	
Azithromycin* Gold Class	P = 0.164	
Azithromycin * Steroid use past year	P = 0.074	Steroid use = less effect
Azithromycin * ICS use at enrollment	P = 0.032	ICS use = less effect
Azithromycin * LABA use at enrollment	P = 0.201	
Azithromycin * LAMA use at enrollment	P = 0.299	

Figure 2 & 3. Albert 2011 hazard ratio for exacerbations patient subgroup analyses.[15] Excerpted from Albert RK, Connett J, Bailey WC, Casaburi R, Cooper JD, Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. *New England Journal of Medicine.* 2011;365(8):689-98.

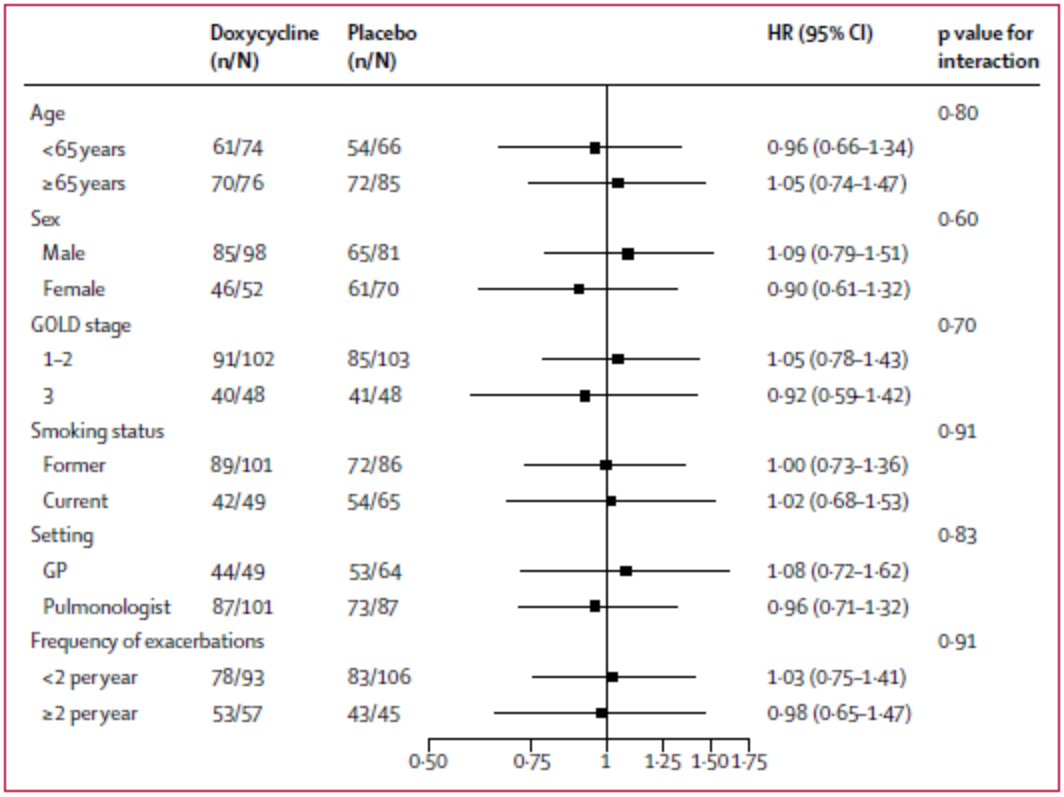


Figure 4. Velzen 2017 hazard ratio for exacerbations patient subgroup analyses.[18] Excerpted from van Velzen P, ter Riet G, Bresser P, Baars JJ, van den Berg BT, van den Berg JW, et al. Doxycycline for outpatient-treated acute exacerbations of COPD: A randomised double-blind placebo-controlled trial. *The Lancet Respiratory Medicine*. 2017;5(6):492-499. doi: 10.1016/S2213-2600(17)30165-0.

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