

# Retrospective Analysis of Doxycycline or Bactrim Prophylaxis for Patients with Chronic Obstructive Pulmonary Disease



**Erik Johnson, Khushboo Verma and Sudhir Sekhsaria\***

Department of Asthma, Allergy and Sinus Center, Medstar Union Memorial Hospital, USA

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\*Corresponding author: Sudhir Sekhsaria, Department of Allergy and Sinus Center, Medstar Union Memorial Hospital Baltimore, USA

## Abstract

**Background:** Azithromycin prophylaxis has shown to decrease COPD exacerbations but led to hearing deficits. Therefore, there is a need to study other antibiotics as possible prophylaxis for COPD exacerbations.

**Objective:** To evaluate the effectiveness of doxycycline or Bactrim prophylaxis for patients with moderate to severe COPD.

**Methods:** We studied patients with moderate to severe COPD who were treated with prophylactic doxycycline or Bactrim in the fall and winter months along with their standard COPD therapy. From patient histories, we determined the number of exacerbations/year and hospitalizations/year prior to and after prophylaxis. Paired t-tests were used to analyze the data.

**Results:** 17 patients with moderate to severe COPD on standard therapy were identified. Prophylactic doxycycline or Bactrim were added to their treatment regimens as a part of routine prophylaxis. Patients were on prophylaxis for a period of 6 months per year. The number of average exacerbations per year decreased from  $4.44 \pm 4.42$  to  $1.20 \pm 1.0$  ( $n=15$ ,  $p=0.0047$ ) and the number of hospitalizations per year decreased from  $1.75 \pm 1.12$  to  $0.00 \pm 0$  ( $n=5$ ,  $p=0.0125$ ). The number of exacerbations per person during the months with prophylaxis was 1.19 compared with 1.63 exacerbations per person during the months without prophylaxis ( $n=16$ ,  $p=0.24$ ). The antibiotics were well tolerated.

**Conclusion:** This retrospective analysis showed a significant decrease in the number of exacerbations and hospitalizations per year for COPD patients undergoing doxycycline or Bactrim prophylaxis. This small study suggests the need for a prospective randomized study evaluating prophylactic doxycycline, Bactrim or other antibiotics in patients with moderate to severe COPD.

**Keywords:** COPD; Bactrim; Doxycycline; Antibiotic prophylaxis

**Abbreviations:** COPD: Chronic Obstructive Pulmonary Disease; SMX-TMP: Sulfamethoxazole and Trimethoprim; CGD: Chronic Granulomatous Disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease

## Introduction

Chronic Obstructive Pulmonary Disease (COPD) has become a worldwide epidemic and continues to be one of the leading causes of morbidity and mortality [1-3]. It is expected to be the third most common cause of death worldwide by 2020 [2]. In 2000, patients with COPD accounted for 8 million physician office and hospital outpatient visits, 1.5 million emergency department visits, 726,000 hospitalizations, and 119,000 deaths [3]. In 2016, the Global Burden of Disease Study reported the prevalence of COPD as 251 million cases. All these lead to increased costs at the individual and societal levels. Frequent exacerbations are associated with a reduced quality of life and possibly with increased depression and anxiety [4,5]. Many COPD exacerbations are due to secondary bacterial infections over viral infections and therefore, preventative treatments with

antibiotics may help improve quality of life of patients, reduce the number of exacerbations and reduce health care costs [6]. It is reported that there is almost a two-fold increase in COPD exacerbations during the winter months [7].

Despite the availability of effective macrolide prophylaxis, the potential side effects of these antibiotics limit their long-term use. Therefore, antibiotics like doxycycline and Bactrim can be considered viable alternatives for prophylaxis against COPD exacerbations. Doxycycline, a tetracycline antibiotic, has been shown to possess anti-inflammatory properties in addition to its antibiotic properties, which could explain its potential effectiveness for chronic inflammatory diseases such as COPD [8]. Furthermore, it has been shown to accumulate in the sputum during its use, which may prevent the colonization of

bacteria and the recurrence of acute infections [9]. More recent studies have shown that doxycycline decreases the production of Interleukin-8, which is an inflammatory cytokine [10]. Bactrim, is a combination of Sulfamethoxazole and Trimethoprim (SMX-TMP), has been shown to be an effective prophylactic agent in diseases such as Chronic Granulomatous Disease (CGD), whereby the number of life-threatening episodes decreased from every 10 months to every 40 months when put on prophylaxis [11]. It has also been proven effective as prophylactic treatment for interstitial pneumonia [12].

Because there is little research regarding the potential effectiveness of different antibiotics with regards to COPD prophylaxis, this study focuses on the effectiveness of doxycycline and Bactrim as potential prophylactic agents.

### Materials and Methods

We conducted a retrospective study to determine effectiveness of alternative antibiotics for COPD prophylaxis. We used patient records to collect all the information needed. We included chronic COPD patients, falling in the moderate to severe categories as per the Global initiative for chronic Obstructive Lung Disease (GOLD) guidelines, with a smoking history of a minimum of 20 pack years, already on the standard COPD therapy prior to the introduction of antibiotic prophylaxis and who received doxycycline or Bactrim prophylaxis for only 6 months in a year. We excluded patients with co-existing lung diseases (none of our patients had asthma), patients on yearlong antibiotic prophylaxis. The patients included represented both genders equally. From the patient histories, the following

### Results

**Table 1:** Demographic Information for Patients in the Analysis.

<b>Number of Patients</b>	<b>n = 17</b>
a) Doxycycline prophylaxis	n = 15
b) Bactrim prophylaxis	n = 2
Number of Patients with hospitalization records	n = 5 (all doxycycline)
Male: Female	8:9
Average Age (Range)	70.7 years old (58:80)
<b>Median FEV<sub>1</sub> % predicted for all patients (Range)</b>	<b>37.04% (16.33:60.88)</b>
a) # Patients with median FEV <sub>1</sub> % predicted ≥ 50% (MODERATE)	n = 2
b) # Patients with median FEV <sub>1</sub> % predicted between 30-50 % (SEVERE)	n = 11
c) # Patients with median FEV <sub>1</sub> % predicted ≤ 30 % (VERY SEVERE)	n = 4
<b>Patients with Standard COPD Treatments during Prophylaxis:</b>	
<b>i. ICS, LABA, and LAMA</b>	<b>n = 15</b>
a) With oxygen treatment	n = 6
b) With theophylline treatment	n = 4
c) With oxygen and theophylline treatments	n = 1
<b>ii. ICS and LABA</b>	<b>n = 2</b>
a) With oxygen treatment	n = 1
b) With theophylline treatment	n = 0

ICS: Inhaled Corticosteroids; LABA: Long-Acting Beta Agonist; LAMA: Long-Acting Muscarinic Antago

17 patients qualified for the study, with fifteen patients on doxycycline prophylaxis and two on Bactrim prophylaxis.

variables were collected: sex, age, COPD therapy, FEV<sub>1</sub> % predicted values, treatment taken, antibiotic prophylaxis used and dates of exacerbations or hospitalizations. We recorded the number of exacerbations while only on standard COPD therapy over a 3 year period, and then when they were put on prophylactic doxycycline (50mg, twice daily) or Bactrim (double strength, once daily) for 6 months, from October 1st to March 30th, for the next 3 years. Exacerbations were defined as any worsening of symptoms or any acute bronchitis episode requiring a course of antibiotics and/or prednisone. Hospitalizations refer to dates on which the patient was hospitalized for symptoms related to COPD. The number of exacerbations and/or hospitalizations during this time period were recorded and divided by the number of years of prophylaxis to get average values. Patients were treated for COPD at four different centers in the Baltimore, MD and greater-DC areas. Adherence to medications was checked every 4-8 weeks.

The primary outcomes for this study were measured as the change in the average number of exacerbations and hospitalizations per year with and without antibiotic prophylaxis (i.e. during the 6-month period after the discontinuation of prophylaxis). The other outcome of interest was the average number of exacerbations per person during months with and without prophylaxis.

In this study, the difference in the number of exacerbations was normally distributed and hence paired t-tests were used for analysis.

Patients were on prophylaxis for 6 months/year for a 3-year period. The demographic data for the patients with average

values for age, FEV1 % predicted and duration of prophylaxis are reported in Table 1. Most patients were treated with a standard COPD therapy, which consists of inhaled corticosteroids, long-acting beta-agonists and long-acting muscarinic antagonists. However, two of the patients were treated without the long-acting muscarinic agonists. Both antibiotics were tolerated well except for some nausea in these first few days of doxycycline treatment. As the prophylactic dose of doxycycline is only half its therapeutic dose, all the patients reported resolution of nausea after the first few days.

The number of average exacerbations per year decreased from  $4.44 \pm 4.42$  to  $1.20 \pm 1.0$  ( $n=15$ ,  $p = 0.0034$ ) before prophylaxis and after the start of prophylaxis respectively (Figure 1). The number of hospitalizations/years decreased from  $1.75 \pm 1.12$  to  $0.00 \pm 0$  ( $n=5$ ,  $p=0.0125$ ) before prophylaxis and after the start of prophylaxis, respectively (Figure 1). None of the patients had reported hospitalizations after they started the prophylaxis.

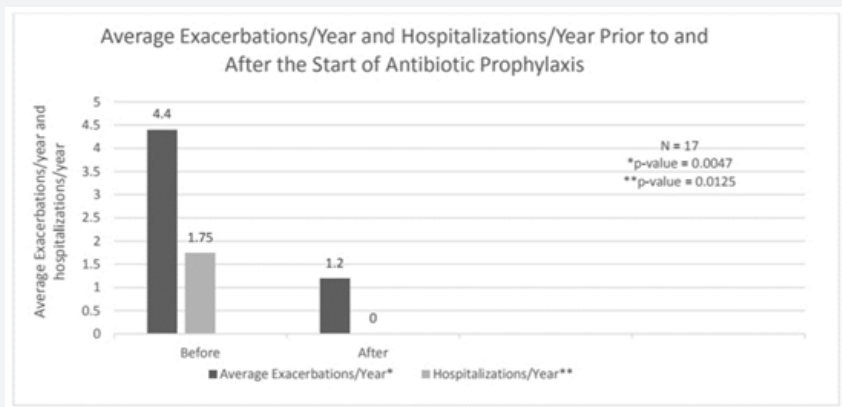
The number of exacerbations/people during the months of prophylaxis was  $1.19 \pm 1.33$  compared with  $1.63 \pm 2.03$  exacerbations/person during the months off prophylaxis ( $n =16$ ,

$p = 0.24$ ). One patient was excluded from this analysis because she was on yearlong Bactrim prophylaxis.

**Discussion**

Macrolide antibiotics, specifically azithromycin and erythromycin, have been shown to decrease the frequency of exacerbations and to improve the quality of life for patients with COPD [6,13]. Albert et al. [6] designed a prospective study, in which subjects received either 250mg azithromycin or placebo daily. Subjects taking azithromycin had fewer acute exacerbations than those in the placebo group and the median time to the first acute exacerbation was significantly longer. However, adverse side effects such as hearing deficits from long-term use of azithromycin were reported in a significant number of patients [6].

We used a retrospective study design, so we did not use a placebo, instead, we did comparative studies on patients while on and off prophylactic antibiotics. We chose to administer antibiotics for a 6-month period during the fall and winter months (in contrast to previous studies in which patients were administered antibiotics all year long) since that is when most exacerbations tend to occur [14].



**Figure 1:** Bar graphs depicting exacerbations/year and hospitalizations/year prior to and after antibiotic prophylaxis.

We found that there was a statistically significant reduction in the number of exacerbations and hospitalizations after the start of prophylaxis with doxycycline or Bactrim for patients with moderate to severe COPD (Figure 1). Doxycycline and Bactrim were tolerated well except for a few cases of mild nausea in the initial days of treatment with doxycycline. However, our small study failed to reach statistical significance for the number of exacerbations and hospitalizations comparing the months on prophylaxis with the months without prophylaxis. With a larger study, the results may show a significant reduction of exacerbations per person during the months when prophylaxis was taken. This approach of using antibiotics for 6 months a year instead of yearlong antibiotics may minimize their potential side effects.

Our study is limited by the small number of study subjects as well as its retrospective nature. Furthermore, COPD

exacerbations are often not reported to physicians [15]. Not reporting certain exacerbations could skew the significance of the data in either direction. Nevertheless, the data reported is very significant for a small study and supports further studies.

**Conclusion**

In summary, we retrospectively analyzed the effectiveness of antibiotics doxycycline and Bactrim as prophylactic agents for patients with moderate to severe COPD. From the analysis, these antibiotics significantly reduced the number of exacerbations/year and hospitalizations/year. This data supports the need for a larger, prospective and well-controlled study that can adequately assess the effectiveness of doxycycline or Bactrim prophylaxis as alternatives to macrolides, in patients with moderate to severe COPD. There is a need for studies to determine the effectiveness of antibiotic prophylaxis specifically in the fall and winter months

versus a yearlong prophylaxis, to compare risks and benefits of half-yearly prophylaxis as compared to yearlong prophylaxis.

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