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Antibiotic Therapy in Preventing Exacerbations of Severe Chronic Obstructive Pulmonary Disease

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Antibiotic Therapy in Preventing Exacerbations of Severe Chronic Obstructive Pulmonary Disease

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Abstract

Chronic obstructive pulmonary disease (COPD) is a progressive disease that has no cure but is treatable. The treatment goal is to have adequate symptom control, decreased exacerbations, prevent hospitalizations and maintain an independent quality of life. The above are attainable by lifestyle changes and pharmacotherapy. The review of literature is to determine if the benefits of long-term antimicrobial therapy outweigh the risks in the treatment of severe COPD. The search included PubMed, Cochrane and Clinical Key databases. Keywords searched include: chronic obstructive pulmonary disease, antibiotics, macrolides, antibacterial, azithromycin, bronchodilators, standard therapy, COPD exacerbations, adverse effects, and long-term. The gold standard for pharmacotherapy consists of bronchodilators (long-acting $beta_2$ agonist (LABA)). Patients with moderate to severe COPD displayed improved quality of life and decreased exacerbations requiring hospitalization (18 fewer per 1000) while using a LABA compared to placebo. As the disease progresses, bronchodilators are not as effective and additional therapy is required which may include long-term antimicrobial therapy. Adding azithromycin to standard therapy for patients with frequent exacerbations showed a 27% reduction in exacerbation frequency. With prolonged use of antimicrobials there is an increased risk of bacterial resistance. However, in doing this research, it was found that bacterial resistance was not noticed between azithromycin (52%) versus placebo (57%), $p = 0.64$. Although long-term antimicrobial therapy is becoming a hot topic, it is imperative that we continue to study the detrimental development of bacterial resistance.

Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic, slowly developing progressive disease that affects millions of people. The patients that suffer from COPD suffer from symptoms including coughing, shortness of breath, wheezing, respiratory infections, and fatigue. These symptoms can range from mild to very severe, and affect each individual differently. As there is no cure for COPD, lifestyle changes and treatments can reduce symptoms. The goals of COPD treatment are focused on slowing the progression of the disease, improving exercise tolerance and ability to stay active, preventing and treating complications and improving overall health. Standard treatment includes smoking cessation, pulmonary rehabilitation, oxygen therapy, and pharmacological therapy (corticosteroids/bronchodilators) (National Heart, Lung, and Blood Institute [NHIBI], 2017).

Statement of the Problem

Patients with severe COPD that have exhausted all modalities of standard treatment, may still suffer from "flare ups" or exacerbations of symptoms which can alter their quality of life and lead to frequent hospitalizations (NHIBI, 2017).

Research Questions

In these severe cases, would adding a macrolide antibiotic to their standard treatment decrease exacerbations and improve overall health and quality of life? Do the benefits of antibiotic therapy outweigh the risks?

Methodology

In an effort to answer the above questions, the chosen studies and review articles included adults (18 years and older), having a history of moderate to very severe COPD, having had one to three acute exacerbations of COPD (AECOPD) in the last year and continuing on

standard therapy for COPD. The studies and review articles with this criteria would provide the best and most unbiased data. Peer reviewed journal articles and online data sets were used in researching and developing this paper. Two of the journal articles are from 2010 and the rest are from 2013-2017. These articles were found in PubMed, Cochrane and Clinical Key databases. MeSH terms searched included: chronic obstructive pulmonary disease, antibiotics, macrolides, antibacterial, azithromycin, bronchodilators, standard therapy, COPD exacerbations, adverse effects, and long-term. These keywords were combined using "AND" to limit the search. The search produced 26 articles pertaining to my topic. There were 16 articles reviewed and included as meta-analysis, narrative reviews, systematic reviews, randomized control trials and cohort studies. The 10 articles excluded didn't focus on long-term (3-12 months) therapy.

Review of Literature

The literature yielded high-quality studies concerning macrolide antibiotics and their effects, benefits, and challenges in preventing and treating AECOPD. A search of peer-reviewed journal articles was performed utilizing several electronic databases. These databases included PubMed, Cochrane, Dynamed and Clinical Key. Several complete articles focusing on the prevention of AECOPD by the means of long-term treatment with macrolides were selected. The articles reviewed include meta-analysis, narrative reviews, systematic reviews, randomized control trials and cohort studies. Additionally, online data sets were used to provide an overview of COPD including pathophysiology, symptoms, stages and standard treatment. All sources used have been reviewed and published within the past seven years and show that the patients that fit this qualification have severe COPD and have at least one to three exacerbations each year. Contraindications of this therapy can occur, with the main risk being antibiotic resistance.

An Overview of COPD - Pathophysiology, Symptoms, Stages and Standard Treatment

COPD is the third leading cause of death in the United States (U.S.), is a major obstructive lung disease that currently affects over 16 million people in the U.S. However, it's estimated that 24 million may have COPD without even knowing it (Lung Institute, 2016). COPD is a progressive disease that makes it hard to breathe. This disease gets worse over time. The rate at which it gets worse is dependent on exposure to irritants such as cigarette smoke, air pollution, chemical fumes, dusts or numerous lung infections (NHIBI, 2017).

In order to understand COPD's effects, there needs to be a basic understanding of how the lungs function. As a person inhales air, it travels down the bronchial tubes inside the lungs. As the bronchial tubes continue into the lungs, they become smaller and more abundant until the end is reached where alveoli exist. All along the walls of the alveoli are capillaries. When air reaches the alveoli, oxygen passes through the alveolar walls into the capillaries. At the same time carbon dioxide (CO_2) gas, moves from the capillaries into the alveoli. This process, called gas exchange, provides oxygen for the body to use for vital functions along with removing the waste product of CO_2. The alveoli inflate and deflate with each breath, and in those diagnosed with COPD, this vital function can be altered, limiting air from flowing in and out normally. The causes affecting this function include: the airways and alveoli lose their elastic quality, the walls between many of the alveoli are destroyed, the walls of the airway become thick and inflamed and the airways make more mucus than usual and can become congested (NHIBI, 2017). Symptoms often worsen over time and can limit the patient's ability to do routine activities. Patients in the severe stage may have extreme trouble performing basic activities like walking short distances, walking up a flight of stairs, cooking, cleaning, eating and taking care of themselves due to shortness of breath.

COPD has no cure yet, and how to reverse the damage to the lungs is unknown. However, treatments and lifestyle changes can help patients feel better, stay more active, and slow the progression of the disease (NHIBI, 2017).

At first, COPD may cause no symptoms or only mild symptoms. As the disease progresses and gets worse, symptoms usually become more severe. Common signs and symptoms of COPD include a productive cough, shortness of breath (especially with physical activity), wheezing and chest tightness. COPD patients often have colds or other respiratory infections such as influenza, or the flu. Influenza can cause serious problems for these patients. Simple viruses such as adenovirus or the cold virus can turn into a life threatening situation such as pneumonia and respiratory failure in a matter of hours. The flu and pneumonia vaccination may reduce the risk of developing those infections. Some of the signs of having a life threatening situation requiring hospitalization are having increased dyspnea, cyanosis due to hypoxia, altered mental status, tachycardia, and the recommended treatment is not helping (NHIBI, 2017).

In determining the severity of a patient's COPD, the clinician will classify them in a stage based on their pulmonary function tests (PFT) and symptoms. A PFT is used to measure lung volumes and function. The three most frequently assessed parameters include forced vital capacity (FVC), forced expiratory volume in one second (FEV_1) and the ratio which is FVC/FEV_1. The PFT results tell the clinician if there is COPD present, what stage it is in and if the treatment plan is working. One way to measure prognosis and life expectancy is through the Global Initiative for Chronic Obstructive Lung Disease (GOLD) system of staging. GOLD uses the FEV_1 test from the PFT to categorize the severity of COPD into stages. The FEV_1 shows the

amount of air the patient can forcefully exhale in one second. COPD has four total stages where airflow becomes more limited with each stage (Lung Institute, 2016).

Table 1

GOLD Stages (Lung Institute, 2016)

Stage One	Mild COPD with FEV_1 about 80 percent or more of normal. COPD commonly causes slight airflow limitations.
Stage Two	Moderate COPD with FEV_1 between 50 and 80 percent of normal. Usually during this stage, most people seek help for COPD symptoms of coughing, wheezing and shortness of breath.
Stage Three	Severe COPD with FEV_1 between 30 and 50 percent of normal. Typically, in this stage, COPD symptoms worsen, causing decreased quality of life.
Stage Four	Very severe COPD with a lower FEV_1 than stage three, or those with stage three FEV_1 and low blood oxygen levels. Generally, this stage is known as end stage COPD, meaning the disease has progressed, lung function has deteriorated and flare-ups could be life threatening.

When a patient presents with symptoms of COPD, there is a process or pathway according to the GOLD guidelines that is followed to assist in diagnosing and treating. First, the patient will have a PFT, depending on those results, severity will be classified into stage one (mild), stage two (moderate), stage three (severe), and stage four (very severe). Once classified into a stage, a pharmacological treatment plan will be developed to get the most symptom improvement. Bronchodilators are known as the gold standard treatment for COPD. Bronchodilators do just what their name states, dilates the bronchial tubes. They do this by

relaxing the smooth muscle fibers surrounding the bronchial tubes allowing more air to be moved in and out of the lungs (NHIBI, 2017). There are two main types of bronchodilators, short-acting beta$_2$ agonist and long-acting beta$_2$ agonist. Short-acting bronchodilators have about a one to two minute onset and a duration of four to six hours. These work very well for as needed or emergent situations. Long-acting bronchodilators have an onset of 10-30 minutes and a duration of 12 hours or more and need to be used at the same time every day. These medications are usually taken via an inhaler device. According to the NHIBI (2017), if a patient is classified in stage one, they will only have a short-acting bronchodilator to use as they feel they need it for shortness of breath or cough. If a patient is classified in stage two, they will have a long-acting bronchodilator to use every day and a short-acting bronchodilator to use when needed. In stage three it will be the same treatment as stage two with an inhaled corticosteroid added for the patients that have increased symptoms. An inhaled corticosteroid is used to help decrease inflammation that can develop inside the bronchial tubes. Stage four patients will have all the treatments of the previous three stages. These patients usually will have supplemental oxygen added to their treatment.

The goals of COPD treatment are focused on slowing the progression of the disease, improving exercise tolerance and ability to stay active, preventing and treating complications and improving overall health. Standard treatment includes smoking cessation, pulmonary rehabilitation, oxygen therapy, and pharmacological therapy (corticosteroids/bronchodilators) (NHIBI, 2017).

The Benefits of Macrolide Antibiotics in Preventing and Treating COPD Exacerbations

COPD is characterized by episodes of exacerbations. In an attempt to establish a uniform definition of exacerbations to be used as an outcome measure in clinical trials, the European

Respiratory Society and the American Thoracic Society task force defined exacerbation as an increase in respiratory symptoms over baseline that usually requires a change in therapy (Miravitlles, 2010). There are mainly two strategies to help prevent acute COPD exacerbations. One strategy is nonpharmacological including smoking cessation, pulmonary rehabilitation, lung volume reduction surgery and an influenza vaccine. The other strategy consists of pharmacological treatment. These include bronchodilators, corticosteroids, n-acetylcysteine and phosphodiesterase-4 inhibitors (Ni et al., 2015). Individuals with COPD who suffer recurrent disease exacerbations are likely to see rapid declines in quality of life, lung function and lifespan. As a result, there is a strong interest in developing approaches that can mitigate this substantial problem. While the spectrum of available COPD treatments provide some benefit; they are insufficient. Additional approaches are sorely needed (Donath, Chaudhry, Hernandez-Aya & Lit, 2013).

The gold standard for pharmacological therapy and treatment of COPD is bronchodilators. This therapy starts with the use of short-acting $beta_2$ agonists (SABA) and advancing to long-acting $beta_2$ agonists (LABA) as COPD progresses. Pharmacological therapy is aimed at relieving symptoms, improving quality of life, slowing the decline in lung function, as well as preventing and treating exacerbations. AECOPD impair patients' quality of life, and a large part of the economic burden of COPD is attributed to the cost of managing exacerbations, particularly those resulting in the use of acute care services, or hospitalizations. Appropriate pharmacological management of the disease is therefore important, particularly for reducing and preventing exacerbations. Kew, Mavergames, and Walters (2013) assessed the effects of LABAs twice-a-day dosing versus placebo for patients with COPD on the basis of clinically important endpoints, primarily AECOPD and quality of life. This meta-analysis compared the

effectiveness and safety of LABAs versus placebo in patients with COPD. Inclusion and exclusion criteria were largely similar across trials. Participants were required to be over the age of 40 and to have a smoking history of at least 10 pack-years. There were twenty-six studies meeting inclusion criteria of randomized control trials (RCT) with a parallel-group design of at least 12 weeks. The studies excluded were cross-over trials and RCT's in which participants had to have asthma as well as COPD. The RCT's recruited participants with a clinical diagnosis of COPD based on the following GOLD guidelines. The guidelines are FEV_1/FVC ratio < 0.7 confirming the presence of persistent airflow limitation, progressive and/or persistent dyspnea, chronic cough, chronic sputum production and history of exposure to risk factors (tobacco smoke, smoke from home cooking and heating fuels, occupational dusts and chemicals). Participants' mean age was similar across trials, ranging from 58.8 to 67.2 years in individual trial arms. Trial participants were most often male (range 50% to 94%, median 75%) and Caucasian (range 46% to 100%, median 92%), mean smoking pack-years ranged from 35.4 to 52.5 and FEV_1 indicated that the populations were of moderate to high disease severity, with baseline means ranging from 32.6% to 54.7%. These 26 studies (including 14,939 people with moderate to severe symptoms of COPD) compared twice-daily LABAs with a placebo or dummy inhaler, showed by moderate-quality evidence that LABAs are effective in the long-term for patients with moderate to severe COPD. Results within studies were described most often after six months of treatment, but some were reported at three months and others after as long as three years. They showed improved quality of life (mean difference (MD) -2.32, 95% confidence interval (CI) -3.09 to -1.54; I^2 = 50%) per St George's Respiratory Questionnaire score and decreased exacerbations including those requiring hospitalization (odds ratio (OR) 0.73, 95% CI 0.56 to 0.95; I^2 = 10%) (18 fewer per 1000). They also had better lung function

(73 mL improvement) than people who had taken placebo (95% CI 48 to 98; $I^2 = 71\%$). However, LABA inhalers did not reduce the number of people who died, and no significant difference was noted in the number who had serious adverse events while taking the medication.

For patients with severe or very severe COPD (FEV_1 <50% predicted) and with repeated exacerbations, corticosteroids are often added to the treatment (Kew et al., 2013). The inflammatory mechanisms involved in the development of AECOPD can be complex. Exacerbations can be precipitated by several factors. Infective causes are known to be the most common factors. Bacterial pathogens are identified in just over 50% of cases and viral around 25%. Non-infective causes such as air pollution and other environmental conditions that increase airway inflammation may account for 15% to 20% of exacerbations. Exacerbations become more frequent and more severe as the severity of COPD increases, although the rate at which they occur may reflect an independent susceptibility phenotype-the "frequent exacerbator" (Walters, Tan, White, & Wood-Baker, 2014).

The acute inflammatory response to airway infection is influenced by both pathogenic and host factors, resulting in increased airway and systemic inflammation. Airway inflammation is significantly increased during AECOPD, and evidence of increased numbers of neutrophils, lymphocytes and eosinophils are seen in airways and in sputum. Theoretical mechanisms for clinical improvement in lung function among patients treated with corticosteroids during exacerbations or "flare-ups" may include reduction in airway inflammation or a decrease in airway edema (Walters et al., 2014).

Systemic corticosteroids, such as prednisolone, prednisone and cortisone, are commonly used in the treatment of patients with exacerbations. This can be done by a short course (seven or less days) or a longer course (seven or more days). The shorter course is preferred due to the

side effects of corticosteroid use. In a meta-analysis by Walters et al. (2014) the shorter course of this treatment was as good as the longer length and caused fewer side effects.

Systemic corticosteroid use in COPD is associated with potential adverse drug effects, including fluid retention, hypertension, diabetes mellitus, cataract development, adrenal suppression, immunosuppression and osteoporosis. Fracture risk is increased, as the rate of vertebral compression fractures in the COPD population experiencing acute exacerbations, especially among older people with longer duration of diseases, is high. Short-term use of systemic corticosteroids in the treatment of patients with exacerbations of COPD also has adverse effect on respiratory and peripheral muscle strength. The risk of adverse drug effects of systemic corticosteroids in COPD rises with increasing frequency of high-dose systemic corticosteroid use and with increasing cumulative exposure (more than 1g) (Walters et al., 2014).

With LABAs being the pharmacological gold standard therapy for moderate to severe COPD with an added inhaled corticosteroid for severe to very severe COPD per the GOLD guidelines, some patients still seem to frequently exacerbate their symptoms. In the cases of exacerbations, systemic corticosteroids are added to help decrease airway inflammation and provide some symptom relief, but this comes with an array of adverse effects. There needs to be a pharmacological therapy that can be added to the treatment plan that will help prevent exacerbations leading to hospitalizations, decreased lung functions, and ultimately decreased quality of life. That therapy may be the use of long-term antibiotics in the prevention of AECOPD.

In a peer-reviewed article by Miravitlles (2010) he tests the quantitative or "fall and rise" hypothesis that may explain the mechanism of chronic bacterial colonization and frequent COPD exacerbations. This may also help explain the relapse that occurs when bacteria is not eradicated

with antibiotic therapy. Repeated exacerbations may be the big reason why patients with severe COPD show an excessive decline in lung function over time (Miravitlles, 2010). Important therapeutic goals for antimicrobial therapy may include the treatment of acute exacerbations and reducing the risk of subsequent bacterial exacerbations. Some patients with a particular phenotype show more susceptibility to recurrent exacerbations only a few weeks after the initial one. This is thought to be possibly caused by ongoing lung and systemic inflammation. Eradication of bacterial colonization, otherwise looked upon as chronic infection in the presence of an inflammatory response, may help decrease the progression of the disease. This chronic inflammation is known to decrease the natural immune defense which may increase the rate of subsequent exacerbations (Wilson, Sethi, Anzueto, & Miravitlles, 2013).

The chronic use of macrolides in COPD treatment has received increased attention lately. Bacterial eradication decreases the inflammatory nature of the airways in turn helping reduce exacerbations. Reports investigating the long-term use of antibiotic treatment in COPD patients revealed a total of seven studies examining continuous therapy. In one study by Seemungal, Wilkinson, Hurst, Perera, Sapsford, &Wedzicha (2014) erythromycin 250 mg twice daily (n = 53) was compared to placebo (n = 56). This 12-month study was a randomized double-blind, controlled trial. Patient demographics at baseline were mean age: erythromycin 67 years; placebo 68 years, current smoker: erythromycin 51%; placebo 45%, FEV_1 predicted: erythromycin 49%; placebo 51%, and greater than three exacerbations in previous year: erythromycin 30%; placebo 34%. The outcomes showed a significant reduction in exacerbation for erythromycin versus placebo (35%) (RR: 0.65, 95% CI: 0.49-0.86; p=0.006), erythromycin reduced the median time to exacerbate (271 versus 89 days) (p=0.02), but no difference between arms in FEV_1. There were no difference in side effects between the arms.

In the last decade, a number of new trials have provided evidence for the long-term use of antimicrobials in COPD patients (Miravitlles & Anzueto, 2015). Recently, in a large definitive study, Albert et al. (2011) investigated the use of 12-month treatment with daily azithromycin in COPD patients with an increased risk of exacerbations (mean age 65 years, FEV_1 predicted 39%). In this study, addition of azithromycin to standard therapy compared to placebo and standard therapy led to a 27% decrease in the frequency of exacerbations (hazard ratio 0.73, 95% CI, 0.63 to 0.84; $P<0.001$), an increase of the median time to exacerbations (266 days (95% CI, 227 to 313) vs 174 days (95% CI, 143 to 215); $p<0.001$). Azithromycin was also shown to reduce exacerbations, hospitalizations, and length of hospital stay in patients with severe COPD (mean age 71 years, FEV_1% predicted 32%, 7.0 exacerbations in previous year) in a 12-month retrospective study. The effects of azithromycin in this study was particularly marked in patients with common potentially pathogenic microorganisms isolated in sputum (i.e. Haemophilus influenza, Streptococcus pneumoniae or Moraxella catarrhalis), reducing exacerbations and hospitalizations by 70% and mean hospital stay by 25 days (Wilson, Sethi, Anzueto, & Miravitlles, 2013). Uzun et al. (2014) aimed to test the hypothesis that patients with COPD whom were treated three or more times in the last year for exacerbations may benefit from maintenance treatment of azithromycin. They conducted a randomized double-blind, placebo-controlled, single-center trial in the Netherlands between 2010 and 2013. They randomly assigned 92 patients to the azithromycin group (n=47) or the placebo group (n=45), of which 41 (87%) versus 36 (80%) completed the study. Eligible patients were 18 years or older and diagnosed with COPD. These patients needed to have received treatment with steroids or antibiotics for three or more exacerbations in the last year. Patients were excluded if they had other respiratory diseases (e.g, asthma or cystic fibrosis); presence of bronchiectasis assessed by

CT scan, maintenance antibiotic treatment, allergy to macrolides, using more than 10mg of prednisone per day, liver disease, heart failure, and the use of drugs that could adversely interact with macrolides causing monitoring to not be undertaken. The azithromycin group recorded 84 exacerbations compared to 129 in the placebo group (0.58, 95% CI 0.42-0.79; p=0.001). The results of this study show that azithromycin maintenance treatment could be recommended for COPD patients who are refractory to standard care. If this treatment is chosen, it is suggested to carefully monitor emergence of macrolide resistance. However, in the review article by Simoens, Laekeman, & Decramer (2013) no difference was found in the prevalence of macrolide resistance between the two groups (azithromycin 52% versus placebo 57%, p= 0.64) in patients who were colonized with respiratory pathogens.

Simoens et al. (2013) critically reviewed the international literature pertaining to the effectiveness and safety of macrolides used in the long-term treatment and prevention of AECOPD. All controlled studies focusing on the prevention of AECOPD with the long-term use of macrolides were used. Random control trials were first priority, but observational studies along with before and after studies were also considered. These studies had to measure impact on number of exacerbations, exacerbations requiring hospitalization, and time to first exacerbation. Studies that examined the impact of inflammatory markers were excluded. Inclusion was restricted to articles published in peer review journals. The highest quality of evidence was collected from a multi-center double-blind random control trial consisting of 1,142 patients. Patient demographics include those greater than 40 years of age with COPD, those using supplemental oxygen or systemic corticosteroids in previous year, and those with a history of being admitted to emergency room or hospital for exacerbation. Patients receiving 250 mg of azithromycin (n = 570) daily for one year or placebo (n = 572). The finding showed that

exacerbation frequency was 1.48 per patient-year with azithromycin and 1.83 with placebo (p=0.01). Hazard ratio for having an exacerbation per patient-year was 0.73 with azithromycin (95% CI, 0.63 to 0.84). Time to first exacerbation was 266 days with azithromycin and 174 days with placebo (p<0.001), and COPD related hospitalizations per patient per year was 0.34 with azithromycin and 0.49 with placebo (p=0.14). In this study, no difference was found in the prevalence of macrolide resistance between the two groups (azithromycin 52% versus placebo 57%, p= 0.64) in patients who were colonized with respiratory pathogens at time of enrollment. The literature review suggests that long-term treatment with azithromycin is generally safe and effective in reducing exacerbations and hospitalizations. This article also discussed the budget impact of long-term azithromycin generated additional expenditures of $595 million, but was associated with hospital savings of $950 million due to fewer exacerbations. This equals a one year savings of $355 million.

Intermittent, pulsed fluoroquinolone antibiotic therapy in COPD patients has been investigated in a study conducted by Sethi et al. (2010). This was a randomized, double-blind, controlled trial with 1,157 participants. Patient characteristics included a mean age (moxifloxacin 66 years and placebo 66 years), current smoker (moxifloxacin 35% and placebo 31%), FEV_1% predicted (moxifloxacin 40% and placebo 41%), exacerbations in previous year (moxifloxacin 2.6 and placebo 2.6). Treatment was moxifloxacin 400 mg (n = 573) and placebo (n = 584) administered once daily for five days, with treatment being repeated every eight weeks for a total of six courses (48 weeks). The rationale for pulsed therapy was mainly driven by the concerns about the emergence of resistance with long-term continuous use of antibiotics. Pulsed therapy would allow time for the normal flora to recover and therefore potentially prevent or delay the emergence of resistant strains. Moxifloxacin was selected for the study based of its

potent in vitro activity against the major COPD pathogens, excellent penetration into respiratory tissues, high oral bioavailability and proven efficacy in increasing the exacerbation-free intervals. Pulsed therapy with moxifloxacin was found to significantly reduce the risk of an exacerbation by 25% in patients with moderate-to-severe COPD (OR 0.75, 95% CI 0.565-0.994, p = 0.046), while in a post-hoc analysis, this reduction was 45% in patients with purulent/mucopurulent sputum at randomization (OR 0.55, 95% CI 0.36-0.84, p = 0.006).

A study by James, Petersen, Nazareth, Wedzicha, & Donaldson (2013) performed in the United Kingdom (UK) in a primary care setting aimed to identify the type and prevalence of long-term antibiotic treatments prescribed to COPD patients, along with the multitude of patient characteristics associated. It is a retrospective cohort study using all practices in The Health Improvement Network (THIN) from the UK primary care databases. Inclusion contents for this study are age 35-89 years with a diagnosis of COPD. The focus was on antibiotic courses lasting greater or equal to six months (long term) to avoid misidentification of repeated antibiotic courses in patients with frequent exacerbations. They took ten days as the maximum courses to be considered continuous. There were 92,576 patients with a clinical record of COPD that participated in this study. These patients were predominantly middle-aged or elderly, with greater than 96% older than 50 years, one-third still smoked, and their mean predicted FEV_1% and FEV_1/FVC ratio suggested that they had COPD. They received 749,412 separate antibiotic prescriptions. A total of 998 long-term courses (greater to or equal to 6 months) were prescribed to 567 patients (0.61%) and were used in the analysis. They received an average of two long-term courses. The three most commonly used long-term antibiotics were oxytetracycline, doxycycline, and penicillin. Being male (OR: 1.46, 95% CI 1.23-1.74; p<0.01), not smoking (OR: 1.97, 95% CI 1.59-2.44; p<0.01), or aged 50-79 years (OR: 1) was associated with a greater

chance of being prescribed long-term antibiotics. The findings showed that patients prescribed long-term antibiotic courses were more likely to have a lower FEV_1, to be aged between 50-79 years, and to be a nonsmoker than patients not prescribed long-term antibiotics. The low proportion of COPD patients receiving long-term antibiotics could be explained by the fact that management guidelines for COPD do not recommend this therapy. It may be that the latest clinical trial data have yet to be fully translated into clinical practice, as we observed that the use of azithromycin and clarithromycin for long-term therapy increased significantly in the last five years.

Ni et al. (2015) hypothesized that prophylactic usage of macrolides are a very good option for severe to very severe COPD patients that frequently exacerbate their symptoms. This is primarily due to its antibacterial and anti-inflammatory properties. The researchers performed a meta-analysis to help prove their hypothesis true. The nine RCTs included 1,666 patients, with ages generally ranging from 65-75 years. Most of them had moderate to severe COPD and had experienced exacerbations before study entry. A total of 830 patients were randomly allocated to the macrolide treatment group (one study for clarithromycin, three for erythromycin and five for azithromycin) and 836 were randomly allocated to the control group. The study duration lasted for 3 months to 12 months and all used intention-to-treat analysis. Patients were excluded if they have genetic diseases such as bronchiectasis, asthma, or cystic fibrosis. Seven studies involving 1,614 patients with one or more exacerbations showed a significant reduction in AECOPD while using macrolide prophylaxis compared to the control group (RR = 0.70; 95% CI: 0.56-0.87; $P<0.01$, $I2 = 66.43\%$). Eight studies involving 1,582 participants reported the rate of exacerbations per patient per year, showing the prophylactic use of macrolides led to a reduction in the rate of exacerbations (RR = 0.58, 95% CI: 0.43-0.78, $P<0.01$, $I2 = 67.8\%$). In addition, a

secondary outcome assessed was hospitalizations. Five studies involving 1,424 patients were evaluated and findings showed no difference in hospitalizations between the macrolide group and the control group. The pooled evidence of this meta-analysis confirms that macrolide prophylaxis significantly reduces the frequency of AECOPD.

There are a number of reasons why macrolides have proved successful in reducing exacerbation frequency. Approximately 50% of patients with COPD have lower airways that are colonized with bacteria which puts them at risk for a higher frequency of exacerbations. COPD patients with frequent exacerbations also have higher inflammatory markers. Macrolides appear to have an anti-inflammatory effect by decreasing neutrophil activity and downregulating cytokine expression in various cell types (James et al., 2013).

The Contraindications and Risks of Macrolide Antibiotics in Preventing and Treating COPD Exacerbations

Trials of antibiotic treatment of stable chronic bronchitis were conducted in the 1950s and 1960s with inconclusive results and, as a result, the prescription of prophylactic antibiotics for COPD has not been recommended due to the controversial efficacy, risk of side-effects and the potential development of bacterial resistance (Miravitlles, 2010). However, these studies were limited by small patient numbers, use of low doses of narrow-spectrum antibiotics, and inadequate efficacy measurements (Miravitlles & Anzueto, 2013). The elephant in the room when it comes to long term antibiotic use is obviously bacterial resistance and certain antibiotics becoming ineffective over time. In some of the studies in this section, there is appropriate evidence to prove this theory correct, but there is also evidence that contradicts that theory.

Antibiotic resistance is a major public health problem world-wide and an international effort is needed to counteract its emergence. Antibiotic consumption is increasingly being

recognized as the main cause of this emerging resistance. Therefore, the recognition of clinical characteristics that identify patients with an AECOPD that can be safely treated without antibiotics is extremely important. Miravitlles and Anzueto (2013) hypothesized that in chronically infected COPD patients, a reduction of bacterial load and/or prevention of new strains may reduce frequency and severity of exacerbations. Although, no agents are currently licensed for such therapy in COPD. The possibility of long-term antibiotic use being beneficial in eradicating bacterial colonization and/or reducing chronic airway inflammation is there, but the evidence supporting this hypothesis is limited. Antibiotic consumption is being recognized as the main cause of resistance. Patients that are ambulatory and classified as mild to moderate COPD with the absence of sputum purulence and a low value of C-reactive protein are associated with high rates of clinical cure without antibiotics. However, patients with severe COPD required increased levels of treatment to prevent exacerbations. This opens the door for the use of long-term antibiotic treatment in these patients. Studies conducted over the last decade have indicated that long-term or intermittent antibiotic use helps decrease exacerbation frequency, hospitalizations, and lengthening the time between exacerbations. However, in the study by Albert et al. (2011) the percentage of resistance to macrolides in respiratory pathogens isolated from nasopharyngeal swabs was greatly increased in the antibiotic population compared to the placebo arm (Miravitlles & Anzueto, 2015).

Donath, Chaudhry, Hernandez-Aya, & Lit (2013) performed a collaborative study to evaluate via a meta-analysis on whether the overall body of research supports the hypothesis that prophylactic macrolides are effective in preventing AECOPD. The initial search yielded 341 studies. Of the 341 studies, six were chosen for inclusion in the meta-analysis. The six studies chosen were conducted within the past 10 years. They included patients with severe to very

severe COPD with baseline FEV_1% values ranging from 20% to 50%. Most patients included in these studies had a history of recurrent AECOPD. Two of the six randomized controlled trials were not blinded; there were otherwise no major study biases that were consistently identified among included studies. The primary end point was the number of exacerbations as a function of person-years. The comprehensive meta-analysis, involving six studies and 1,677 patients, showed that there was 37% relative risk reduction (RR: 0.627, 95% CI: 0.452-0.868 p-value: 0.005) in exacerbations among patients taking macrolides compared to those taking a placebo. However, in terms of relative risk of having some adverse effects leading to study withdrawal, all six studies addressing that outcome found 95% increased risk of withdrawal due to adverse event among patients taking prophylactic macrolides compared to those taking placebo (RR: 1.95, 95% CI 0.92-4.14, p-value: 0.08). In the article by Miravitlles & Anzueto (2013) erythromycin 250 mg twice daily for one year showed a reduction of 35% in exacerbations compared to placebo, but increased the risk of significant gastrointestinal symptoms including nausea, vomiting, abdominal cramps, and diarrhea. This drug also has significant interaction with drugs that are metabolized by the liver via the cytochrome P-450 enzyme system Bacterial eradication decreases the inflammatory nature of the airways in turn helping reduce exacerbations. In contrast, treatment with moxifloxacin has been efficacious in bacterial eradication in the airway, but new strains appeared again in eight weeks, indicating that recolonization is frequent in certain patients with COPD (Miravitlles, 2010). In general, quinolones are well tolerated and have an adverse event rate of approximately 4-5%. These adverse effects, which are generally mild and transient, include rash, dizziness, headache, gastrointestinal disturbances (usually nausea, vomiting, dyspepsia, diarrhea, abdominal pain, etc.), and minor hematological

abnormalities (Miravitlles & Anzueto, 2013). There can be relapse of symptoms if antibiotic therapy does not eradicate bacterial colonization or resistance develops.

Long-term azithromycin therapy has been shown to reduce exacerbations of COPD and is recommended by recent society guidelines for use in COPD patients who are at risk for recurrent exacerbations. However, concerns about adverse effects have limited its widespread adoption. Physicians deciding whether to use long-term azithromycin therapy must weigh each patient's individual risk of cardiovascular complications and both the individual and population impact of macrolide resistance against the expected benefit (Parks-Taylor, Sellers, & Taylor, 2015). Parks-Taylor et al. (2015) reviewed the literature on the effectiveness and safety of chronic azithromycin for the prevention of AECOPD. A 2013 Cochrane review compiled seven studies evaluating the use of at least moderate severity of airflow limitation participants. Although there were only two studies that specifically evaluated azithromycin, the results showed prophylactic use of macrolides reduced AECOPD. However, on the other side of the argument, broad adoption of this treatment has stalled due to concerns of adverse effects. Although Albert et al. (2011) found that hearing loss was more prevalent in patients receiving azithromycin than placebo (25% vs. 20%), the hearing decrement resolved in one-third of these patients while they were still taking azithromycin. In a very large cohort of Tennessee Medicaid patients, Ray and colleagues (2012) demonstrated increased cardiovascular (hazard ratio, 2.88; 95% CI, 1.79 to 4.63; $P<0.001$) and all-cause mortality (hazard ratio, 1.85; 95% CI, 1.25 to 2.75; $P=0.002$) during azithromycin therapy compared to placebo. In the study by Albert et al. (2011) the percentage of resistance to macrolides in respiratory pathogens isolated from nasopharyngeal swabs was greatly increased in the azithromycin population compared to the placebo arm. In that same study, azithromycin decreased the number of patients colonized by respiratory flora, but also

showed that fewer patients receiving azithromycin became colonized with macrolide-resistant organisms than the group receiving placebo. If this treatment is chosen, it is suggested to carefully monitor emergence of macrolide resistance. However, in the review article by Simoens et al. (2013) no difference was found in the prevalence of macrolide resistance between the two groups (azithromycin: 52% versus placebo: 57%, p= 0.64) in patients who were colonized with respiratory pathogens. Although azithromycin holds much promise in the prevention of AECOPD, the benefits don't come without penalty. Azithromycin has the potential to do much good, but judicious use will be necessary to avoid the bad and the ugly (Parks-Taylor et al., 2015).

It is evident that further studies are needed to estimate the potential risks of antibiotic prophylaxis in terms of long-term adverse effects, the development of potential resistance, and to assess whether the benefits outweigh the risks (Miravitlles & Anzueto, 2015).

Discussion

COPD is a complex disease process that can require a complex treatment plan. As per the GOLD guidelines, it is classified in four different stages and treated according to the stage that classifies the patient. This is a good guide for treating the patients that classically present into each stage and are maintained on the recommended therapy. When the recommended therapy no longer is effective and the patient declines, what can providers do to help? Long-term antibiotic therapy is becoming one of the most talked about treatments amongst pulmonary specialists. Current research indicates there is significant improvement in symptom exacerbation for the patients using this therapy including: decreased number of exacerbations, decreased hospitalizations and improved quality of life. Anytime antibiotic use is considered an option, the fear of adverse effects, especially bacterial resistance, becomes a concern.

In patients with severe COPD, are standard pharmacological methods of therapy enough to prevent exacerbations?

COPD is currently the third leading cause of death in the U.S. and shows no signs of declining. It is a progressive disease that can be treated and controlled, but not cured. Due to that fact, the objective for treatment of COPD is to reduce or slow progression and improve quality of life. In order to accomplish these goals lung function needs to be sustained. Lung function can decline by continued cigarette smoking, inactivity, continued exposure to irritants and fumes, obesity, and chronic infections. These negative effects on lung function happen because when breathing in and out, air moves in and out. The airways and air sacs inside the lungs are very elastic and stretchy allowing that oxygen carrying air to move in and out of the lungs. When an individual is exposed to the aforementioned environmental effects, it causes the airways and air sacs to lose that elasticity and lose the ability to move an adequate amount of air in and out. Symptoms such as dyspnea, chronic cough, chronic phlegm production, and repeated lung infections usually increase over time.

The severity of this disease is based on stages. These stages range from one (mild) to four (very severe) (Lung Institute, 2016). The classification is determined by the FEV_1. Treatment is then based on the classification of stage the patient is in. If diagnosed in stage one, a patient may notice only slight airflow limitations and require a SABA for pharmacological therapy to use as needed. A stage two (moderate) classification requires a LABA to be used twice per day and a SABA as needed. Stage three (severe) treatment will be the same as stage two with an inhaled corticosteroid added. The stage four (very severe) patients are the ones that require all the treatments of the first three stages but may require supplemental oxygen, oral

systemic corticosteroids, phosphodiesterase-4 inhibitors or long-term antibiotic therapy (NHIBI, 2017).

The gold standard for pharmacological therapy and treatment of COPD is bronchodilators. This therapy starts with the use of SABAs and advancing to LABAs as COPD progresses. AECOPD impair patients' quality of life, and a large part of the economic burden of COPD is attributed to the cost of managing exacerbations, particularly those resulting in the use of acute care services or hospitalizations. Appropriate pharmacological management of the disease is therefore important, particularly for reducing and preventing exacerbations. Kew, Mavergames, and Walters (2013) assessed the effects of LABAs twice a day dosing versus placebo for patients with COPD on the basis of clinically important endpoints, primarily COPD exacerbation, and quality of life. The treatment time ranged from three months to three years with a large number of patients used. Although there were a large number of patients, it was limited to mainly Caucasian males. The LABA group showed improved quality of life (mean difference (MD) -2.32, 95% confidence interval (CI) -3.09 to -1.54; I^2 = 50%) per St George's Respiratory Questionnaire score and decreased exacerbations including those requiring hospitalization (odds ratio (OR) 0.73, 95% CI 0.56 to 0.95; I^2 = 10%) (18 fewer per 1000). They also had better lung function (73 mL improvement) than people who had taken placebo (95% CI 48 to 98; I^2 = 71%). This study provided by moderate-quality evidence that LABAs are effective in the long-term for patients with moderate to severe COPD.

If and when patients have progressed to stage three or four and are suffering from repeated exacerbations, corticosteroids are an addition to the standard therapy. The inflammatory mechanisms underlying the onset and development of AECOPD are complex, and may be precipitated by several factors including air pollution and other environmental

conditions. These can increase airway inflammation and may account for 15% to 20% of exacerbations. Corticosteroids are designed to decrease airway inflammation in an attempt to improve lung function during an exacerbation (Walters, Tan, White & Wood-Baker, 2014).

In a meta-analysis by Walters et al. (2014) comparing the efficacy of short duration (seven or fewer days) and conventional longer-duration (longer than seven days) systemic corticosteroid treatment of adults with AECOPD proved their hypothesis correct in that there were no difference. In this particular meta-analysis the definition of an acute exacerbation could include any combination of an increase in breathlessness, sputum volume, sputum purulence, cough or wheeze. The downfall to this study appears to be the definition of an exacerbation. Many COPD patients have increased cough and volume of sputum but are not exacerbating their symptoms and requiring systemic corticosteroids. This may mean that some patients were being inappropriately treated with systemic steroids. The risk of adverse drug effects of systemic corticosteroids in COPD rises with increasing frequency of high-dose systemic corticosteroid use and with increasing cumulative exposure (more than 1g).

In patients with severe COPD, what are the benefits of adding a long-term macrolide antibiotic to standard therapy?

When a patient's COPD advances to the severe to very severe stages, standard therapy is continued, but doesn't always do a very good job of preventing exacerbations. Systemic steroids are added to help improve lung function during the exacerbation but recommended long-term to help prevent exacerbations. A not-so-new, but revisited therapy, is being talked about in benefiting severe COPD patients who frequently exacerbate their symptoms. That therapy may be the use of long-term antibiotics in the prevention of AECOPD.

In an attempt to test his hypothesis of chronic bacterial colonization leading to AECOPD, Miravitlles (2010) performed a meta-analysis. One study he noted by Seemungal et al. (2014) using erythromycin 250 mg twice daily (n = 53) compared to placebo (n = 56) for a treatment length of twelve months showed a significant reduction in exacerbation for erythromycin versus placebo (35%) (p=0.006), erythromycin reduced the median time to exacerbate (271 versus 89 days) (p=0.02), but no difference between arms in FEV_1. There were no difference in side effects between the arms. Albert et al. (2011) performed a study adding azithromycin to standard therapy in COPD patients with an increased risk of exacerbations. The addition of azithromycin lead to a 27% decrease in the frequency of exacerbations. Uzun et al. (2014) found that azithromycin was used as a maintenance treatment for patients that suffered three or more exacerbations in the last year. The azithromycin group recorded 84 exacerbations compared to 129 in the placebo group. The negatives to this study include a small sample size with a broad age population and included only one health center. Although, it was a three year study with a high completion percent and they eliminated a lot of other crossover factors that could obscure results.

In the article by Simoens et al. (2013) patients received 250 mg of azithromycin (n = 570) daily for one year or placebo (n = 572). The finding showed that exacerbation frequency was 1.48 per patient-year with azithromycin and 1.83 with placebo (p=0.01) along with time to first exacerbation being 266 days with azithromycin and 174 days with placebo (p<0.001).

Intermittent, pulsed fluoroquinolone antibiotic therapy in COPD patients have been investigated in a study conducted by Sethi et al. (2010). Moxifloxacin given for five days per week for 48 weeks reduced the risk of an exacerbation by 25% in patients with moderate-to-severe COPD, while this reduction was 45% in patients with purulent/mucopurulent sputum at

randomization. This study showed that those patients with purulent sputum may benefit more from the use of pulsed long-term antibiotic therapy compared to those without.

In a 2015 meta-analysis performed by Ni et al. (2015) the use of prophylactic macrolides was a very good option for severe to very severe COPD patients who frequently exacerbate their symptoms. This study had good exclusion criteria including bronchiectasis, asthma or cystic fibrosis helping to prevent any crossover effects. Patients with one or more exacerbations showed a significant reduction in AECOPD while using macrolide prophylaxis along with leading to a reduction in the rate of exacerbations. In contrast, a secondary outcome assessed was hospitalizations. These findings showed no difference in hospitalizations between the macrolide group and the control group.

In patients with severe COPD, what are the risks and contraindications of adding a long-term macrolide antibiotic to standard therapy?

Chronic or long-term use of antibiotics will always bring up a concern for bacterial resistance. This is an appropriate concern and should be analyzed anytime there is antibiotic use. The following section of this paper is dedicated to analyzing the risks, adverse effects, contraindications etc. to long-term antibiotic use.

The use of long-term antibiotics dates back to the 1950s and 1960s and bacteria becoming resistant to antibiotics was a concerning issue in the US (Miravitlles & Anzueto, 2013). That same concern remains in 2018. If inappropriate antibiotic prescribing isn't controlled, many medications will lose their effects on fighting bacterial infections. Therefore, the recognition of clinical characteristics that identify patients with an AECOPD that can be safely treated without antibiotics is extremely important. In an article by Miravitlles & Anzueto (2013) it is felt that patients whom are ambulatory and classified as mild to moderate COPD with

the absence of sputum purulence and a low value of C-reactive protein are associated with high rates of clinical cure without antibiotics. As stated in the previous section, long-term antibiotics show benefit in preventing exacerbations in severe to very severe COPD. However, Albert et al. (2011) took nasopharyngeal swabs from patients in a long-term azithromycin group and placebo group showing that the azithromycin group had more resistance to macrolides in respiratory pathogens.

In a collaborative meta-analysis performed by Donath, Chaudhry, Hernandez-Aya, & Lit (2013) involving six studies and 1,677 patients, the researchers found that there was 37% relative risk reduction in exacerbations among patients taking macrolides compared to placebo. However, all six studies showed a 95% increased risk of withdrawal from the studies due to adverse effects among the macrolide group compared to placebo. In studies using erythromycin, adverse effects consisted of significant gastrointestinal symptoms. It also may be contraindicated due to its interaction with drugs that are metabolized by the liver via the P-450 enzyme system (Miravitlles & Anzueto, 2013).

Concerns about the adverse effects, mainly bacterial resistance has limited the widespread adoption of long-term antibiotic therapy. If a physician is debating on starting this therapy or not, he or she needs to assess the individual's risk for cardiovascular complications and impact of macrolide resistance against expected benefit. Albert et al. (2011) found that there was greater hearing loss in individuals receiving azithromycin (25%) compared to the placebo (20%). In the azithromycin group, the hearing loss resolved in one-third of those affected while they were still taking it. In a cohort of Tennessee Medicaid patients, Ray and colleagues (2012) showed an increase in cardiovascular and all-cause mortality with azithromycin compared to placebo. It was proposed to exclude patients from long-term antibiotic therapy that have QT_c >

450ms, co-administration of QT prolonging medications, heart failure, coronary artery disease, peripheral vascular disease, cerebrovascular disease, or tachycardia. In the study by Albert et al. (2011) respiratory pathogens resistant to macrolides were significantly increased in the azithromycin group compared to placebo. However, it also showed that the placebo group became more colonized with macrolide-resistant organisms than the azithromycin group. If long-term macrolide therapy is chosen, it is suggested to monitor bacterial resistance. Although, in the article by Simoens et al. (2013) no difference was found in the prevalence of macrolide resistance between the two groups (azithromycin: 52% versus placebo: 57%, p= 0.64) in patients who were colonized with respiratory pathogens.

In discussing the controversial subject of the benefits to long-term antibiotic therapy compared to the risks, contraindications and adverse effects will probably continue on and off for many years. As discussed in this paper, the data is proving the benefit, but it needs to be used in an appropriate patient population. With all patients involved in this therapy, bacterial resistance is the main risk and concern. The risks and adverse effects may be a reason a particular patient should not be prescribed this therapy. It is the responsibility of the provider to weigh the risk to benefit scenario. Due to this therapy becoming more widely used than in the past, there needs to be more extensive studies involving benefits versus risks.

Applicability to Clinical Practice

As stated in this paper by the recent research done, long-term antibiotic use for the prevention and treatment of AECOPD is being minimally used at this point. This is becoming a much more talked about and performed practice in a certain COPD patient population. In discussing this topic with Val Tomhave, RRT and supervisor of the Sanford Pulmonary Rehab. It was discovered that long-term antibiotic therapy is becoming a more frequent treatment for the

patient population consisting of severe to very severe COPD with frequent exacerbations. Frequent meaning up to three per year or requiring hospitalization one to two times per year. She states that three of her patients with severe to very severe COPD are currently using long-term azithromycin therapy with great success. These patients were frequently exacerbating which at times involved hospitalization. They were finding themselves on and off antibiotics regimens and needing the assistance of systemic corticosteroid bursts regularly without feeling complete recovery (V. Tomhave, personal communication, November 10, 2017). That in itself can be a big contributor to antibiotic resistance, not to mention the adverse effects of prolonged use of systemic steroids. While on the long-term azithromycin used indefinitely three times per week, they have been suffering less exacerbations, decreased recovery time from exacerbation, no hospitalizations and a greatly improved quality of life. This was not a study or any data collected, but just an unbiased observer realizing the improved outcomes of her patient population. She states that this therapy has only been utilized by pulmonary specialists in her patients, but in her anecdotal opinion, it will gain steam in family practice as it is more extensively studied (V. Tomhave, personal communication, November 10, 2017).

The use of prophylactic antibiotics in COPD is a clear example of a decision that has to be made based on a careful evaluation of a risk-benefit analysis. There is no doubt that antibiotic prophylaxis reduces exacerbation frequency in selected populations of COPD patients, but it is also clear that long-term use of antibiotics is associated with potentially serious adverse events and increased risk of bacterial resistance; therefore, both pros and cons must be evaluated in a case by case indication (Miravitlles & Anzueto, 2015).

The majority of COPD patients (up to two thirds) are non-exacerbators, therefore, not candidates for long-term antibiotics. Regarding the third of COPD patients with frequent

exacerbations, it is crucial to understand that there are different phenotypes of exacerbators such as the inflammatory, eosinophilic, bacterial, viral and pauci-inflammatory. Exacerbations associated with eosinophilic inflammation can potentially be prevented effectively with inhaled corticosteroids while pauci-inflammatory exacerbations should respond to optimal bronchodilation and rehabilitation. Infective exacerbations may not be completely prevented by bronchodilators or anti-inflammatories. Patients suffering from frequent or severe infective exacerbations despite optimal pharmacological and non-pharmacological treatment would be candidates for long-term antibiotic treatment. This is a treatment for a selected minority of patients with particularly severe COPD at high risk of severe infective exacerbations (Miravitlles & Anzueto, 2015). It is possible that the benefit of long-term antibiotic treatment may be due to the eradication of bacterial colonization and reduction in chronic airway inflammation. With that being said, this project has proven that long-term antibiotic therapy has proven beneficial in the appropriate patient population and prevents exacerbations which in turn saves medical dollars.

Primary care providers will inevitably play a pivotal role in the use of this therapy. Currently, the subject of prolonged antibiotic use and bacterial resistance, is probably in the hands of pulmonary specialists. The one-third of the COPD population that falls into the category of being eligible for long-term antibiotic therapy is already diagnosed, presenting with symptoms and have exhausted standard therapy. Specialists most likely have taken over their pulmonary care and will decide appropriateness for therapy. Due to the large push for preventative medicine, primary care will probably figure into this equation. They will be a major factor in preventing patients from escalating to the stage of needing long-term antibiotic therapy. This will include helping patients with smoking cessation, eating a healthy diet, getting regular cardiovascular exercise and overcoming psychosocial barriers to accomplish a healthy lifestyle.

There is an obvious realization that not all patients will follow those recommendations, but education early and often will help improve outcomes. Primary care is the quarterback for each patient's team and has to offer that leadership for preventative medicine to work.

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