

# Long term Azithromycin role in severe Chronic Obstructive Pulmonary Disease

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**Abstract-** Exacerbations of COPD have a major impact on the course of the disease. Frequent exacerbations can result in lower quality of life, faster in decline in lung function, higher mortality rate and has a major impact on the health care budget. Maintenance treatment with azithromycin during a period of one year resulted in a significant decrease in COPD exacerbations during that year. However, there is little information about the long-term effect of azithromycin maintenance treatment for more than one year.

**Aim of the study is to identify the Role of Azithromycin in COPD. Methodology-** Cross sectional study.

**Result and conclusion:** There was a significant reduction in acute exacerbation and length of hospital stay in patients with Severe COPD on Azithromycin.

**Index Terms—** Azithromycin, Chronic Obstructive Pulmonary Disease, Exacerbations

## INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (COPD) result in frequent visits to physicians' offices and emergency rooms and numerous hospitalizations and days lost from work; they also account for a substantial percentage of the cost of treating COPD. Patients who have acute exacerbations of COPD, as compared with patients with COPD who do not have acute exacerbations, have an increased risk of death, a more rapid decline in lung function, and reduced quality of life. Although inhaled glucocorticoids, long-acting beta<sub>2</sub>-agonists, and long-acting muscarinic antagonists reduce the frequency of acute exacerbations of COPD, patients receiving all three of these medications may still have acute exacerbations, on average of 1-4, each year.

Macrolide antibiotics have immunomodulatory, anti-inflammatory, and antibacterial effects. Seven small studies that tested whether macrolides decrease the frequency of acute exacerbations of COPD reported conflicting results. Accordingly, we conducted a large, randomized trial to test the hypothesis that azithromycin decreases the frequency of acute exacerbations of COPD when added to the usual care of these patients.

Acute exacerbations of chronic obstructive pulmonary disease (COPD) are a frequent event during evolution of the disease,<sup>1</sup> and the mortality risk increases with its frequency, especially when patients require hospitalization.<sup>2,3</sup> Previous studies using protected specimen brushing have shown that bacterial infection could be the etiology in approximately 50% of acute exacerbations of COPD (AECOPD).<sup>4</sup> However, it is sometimes difficult to distinguish colonization from infection when organisms are found in sputum cultures from COPD patients.

Recently, interest in the use of prophylactic antibiotics to prevent AECOPD has increased, and macrolides in this setting have the advantage of having both antibacterial and anti-inflammatory properties. Long-term macrolide therapy is routinely used in two diseases, ie, diffuse panbronchiolitis and cystic fibrosis, both of which involve chronic airway inflammation. Erythromycin is the most commonly used macrolide in diffuse panbronchiolitis, and obtains notable improvements in symptoms and survival. Studies in cystic fibrosis have mostly used azithromycin and have found improvement in lung function and a reduced exacerbation frequency. These effects are probably due to modulation of the inflammatory response and its ability to impede formation of biofilm. Azithromycin has also been shown to be useful in the treatment of patients with bronchiectasis and chronic bronchial infection by *Pseudomonas aeruginosa*.

Given the importance of inflammation and bacterial infection in the pathogenesis of COPD, it has been proposed that macrolides may offer unique advantages as disease-modifying agents. Only two studies to date have analyzed the effectiveness and safety of long-term erythromycin in COPD over a 12-month period, reporting a significant reduction in moderate to severe AECOPD. It remains to be established whether the therapeutic effect of erythromycin reflects antimicrobial activity, an immunomodulatory effect, or both. Preliminary data have recently been reported for the MACRO study, a randomized controlled trial evaluating the utility of long-term azithromycin therapy to reduce AECOPD, with promising results. Compared with erythromycin, the prototypical 15 member-ring macrolide, azithromycin, appears to have a better safety profile in long-term use, as well as improved bacteriological activity.

In this study, we investigated: the usefulness of long-term intermittent azithromycin therapy in reducing exacerbation frequency in severe COPD patients at a high risk of AECOPD despite conventional maximum treatment.

### AIM OF THE STUDY

To study the role of long term use of Azithromycin in severe chronic obstructive pulmonary disease.

### MATERIALS AND METHOD PATIENT SELECTION

We identified a cohort of 100 patients with severe COPD, with a postbronchodilator forced expiratory volume in one second (FEV<sub>1</sub>) <50% of predicted and routinely controlled at the respiratory day care unit between April 2021 to May 2022. Patients with chronic bronchitis who had repeated AECOPD (at least four exacerbations in the previous year) or chronic bronchial colonization by *P. aeruginosa* treated with longterm azithromycin therapy were recruited for this study. Patients with asthma, significant bronchiectasis, malignancy, unstable heart disease, or liver disease were excluded.

### Study design

Retrospective analysis of data for the year before initiation of long-term azithromycin therapy (for 12 months) in patients with severe COPD was undertaken in order to assess the clinical benefits of this treatment to reduce AECOPD frequency. Azithromycin (one 500 mg tablet) was administered three times per week (Monday, Wednesday, Friday), in accordance with standard practice in patients with bronchiectasis associated with cystic fibrosis and chronic bronchial colonization by *P. aeruginosa*.

Patients were classified into three groups according to the potentially pathogenic microorganisms isolated from their sputum samples during AECOPD in the year prior to azithromycin therapy, ie: Group 1, patients with at least two positive cultures for common potentially pathogenic microorganisms (*Haemophilus influenzae*, *Streptococcus pneumoniae*, *Moraxella catarrhalis*); Group 2, patients with chronic bronchial colonization by *P. aeruginosa* (at least three consecutive sputum cultures for potentially pathogenic microorganisms during a 6-month period of stability); and Group 3, patients whose cultures alternated between being positive for common potentially pathogenic microorganisms and *P. aeruginosa* during exacerbations but without chronic bronchial colonization by this bacteria.

We compared the following parameters overall and by group before and after the 12-month azithromycin treatment period: number of registered AECOPD; number of hospitalizations due to respiratory disease; and length of hospital stay. We also traced the evolution of positive cultures for potentially pathogenic microorganisms during AECOPD in each group and the development of resistance to azithromycin before and after long-term therapy.

### SAMPLING TECHNIQUE

Consecutive, Convenient sampling

### STUDY DESIGN

Retrospective study

### STUDY SETTING

Sri Lakshmi Narayana Institute of Medical Sciences

### STUDY PERIOD

April 2021- May 2022

### Methodology

Sputum samples were collected from all patients for each AECOPD and were processed locally for Gram stain and bacteriological culture. Identification and antibiogram were performed on all bacterial isolates following standardized microbiological protocols. Positive cultures for *P. aeruginosa* during AECOPD were followed by performing additional sputum cultures to identify chronic colonization, diagnosed when three or more consecutive sputum cultures for this potentially pathogenic microorganism were found over a period of 6 months in clinically stable patients, in samples separated by at least 1 month.

### Statistical analysis

All the information was entered into a database and analyzed using SPSS version 26 (SPSS Inc, Chicago, IL). Quantitative variables are expressed as mean  $\pm$  standard deviation, and categorical variables as absolute and relative frequencies. The frequency and length of exacerbations and the microbiology of the sputum cultures before and after azithromycin treatment were compared. Statistical analysis was performed using the Student's *t*-test for paired data and Chi-square tests as required. All statistical tests were performed with a confidence level of 95%.

### Results

Twenty-four eligible patients with severe COPD and frequent AECOPD from the cohort of 100 patients controlled at the respiratory day care unit agreed to participate in this study. Baseline variables for the long-term azithromycin treatment group are shown in [Table 1](#). Ten of 24 patients (41.6%) had no detectable bronchiectasis on high-resolution computed tomography. The median  $\pm$  standard deviation of total bronchiectasis score was  $3.3 \pm 3.5$  (range 0–9).

*Table 1*

Baseline variables of the first year of follow-up for the long-term azithromycin therapy group

Baseline variables (year 1 of follow-up)	Mean (SD)
Age (years)	70.9 (7.4)
FEV <sub>1</sub> , L	0.9 (0.2)
FEV <sub>1</sub> , % predicted	32.2 (9.3)
FVC (L)	2.4 (0.5)
FEV <sub>1</sub> /FVC (%)	39.6 (9.6)
Number of AECOPD/previous year	7.0 (3.0)
Number of hospitalization/previous year	3.3 (2.0)
Days of hospital stay/previous year	43.0 (26.2)
	<b>n (%)</b>
Very severe COPD (GOLD IV)	11 (46)
Chronic bronchitis	24 (100)
Current smoker	0 (0)
Male	24 (100)
Chronic oxygen therapy	5 (20.8)
<i>Pseudomonas aeruginosa</i> colonization	9 (37.5)

**Abbreviations:** COPD, chronic obstructive pulmonary disease; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; FEV<sub>1</sub>, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; SD, standard deviation.

After initiation of azithromycin, four patients did not complete the scheduled 12-month antibiotic treatment period. One was withdrawn for mild dyspepsia, one because of a diagnosis of malignancy during follow-up, and the other two discontinued the treatment prematurely as a personal decision in the absence of reported side effects. No significant adverse events were observed among the 20 patients who completed the 12-month treatment period. One patient died in hospital as a result of an AECOPD during the last month of follow-up.

In the 12 months prior to the start of azithromycin, the 20 study participants had a total of 136 AECOPD, of which 72 (52.9%) were severe and required hospitalization. Long-term azithromycin therapy achieved statistically significant reductions in AECOPD from 136 to 57 (a 58.9% decrease) and hospitalizations from 72 to 28 (a 61.2% decrease) and a reduction of 18.7 days in yearly mean hospital stay due to respiratory disease (see [Table 2](#)).

**Table 2**

Number of AECOPD, hospitalizations due to respiratory disease, and days of hospitalization with and without azithromycin, overall and according to the group of potentially pathogenic microorganisms isolated from sputum samples before initiation of azithromycin

Variable Overall (n = 20)	0–12 months with azithromycin		12–24 months without azithromycin		with % Red	P
	Total	Mean ± SD	Total	Mean ± SD		
Exacerbations (n)	136	6.8 ± 2.8	57	2.8 ± 2.5	58.9	0.000

Variable Overall (n = 20)	0–12 months without azithromycin		12–24 months with azithromycin		% Red	P
	Total	Mean ± SD	Total	Mean ± SD		
Hospitalizations (n)	72	3.6 ± 1.9	28	1.4 ± 1.5	61.2	0.001
Hospital stay (days)	874	43.7 ± 21.4	500	25.0 ± 32.2	42.8	0.013
Common PPM group (n = 7)						
Exacerbations (n)	63	9.0 ± 2.3	19	2.7 ± 2.2	70	0.00
Hospitalizations (n)	29	4.1 ± 2.6	9	1.2 ± 1.4	70.8	0.04
Hospital stay (days)	309	44.1 ± 17.5	133	19 ± 25	57	0.05
<i>Pseudomonas aeruginosa</i> group (n = 9)						
Exacerbations (n)	42	4.6 ± 2.2	24	2.6 ± 2.0	43.5	0.04
Hospitalizations (n)	31	3.4 ± 1.6	17	1.8 ± 1.7	47.1	0.08
Hospital stay (days)	454	50.4 ± 23.9	306	34.0 ± 38.5	32.5	0.23

**Abbreviations:**

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PPM, potentially pathogenic microorganisms; SD, standard deviation; % Red, percentage reduction.

On the basis of potentially pathogenic microorganisms isolated in sputum samples during the year prior to starting azithromycin, seven patients with common potentially pathogenic microorganisms were included in Group 1, nine patients with chronic bronchial colonization by *P. aeruginosa* in Group 2 (of whom five [55.5%] were receiving inhaled colimycin therapy), and four patients with exacerbations due to common microorganisms and *P. aeruginosa* in Group 3. Long-term azithromycin therapy reduced the number of AECOPD, hospitalizations, and days of hospital stay in all groups. This reduction was particularly significant in Group 1 (common potentially pathogenic microorganisms) with a 70% reduction in AECOPD and hospitalizations, and a mean reduction of 25 days in mean hospital stay. In the group colonized by *P. aeruginosa*, a statistically significant reduction in AECOPD of 43.5% was observed, the number of hospitalizations fell by 47.1%, and their hospital stays by 32.5%, although these differences did not reach statistical significance. The group alternating between common potentially pathogenic microorganisms and *P. aeruginosa* during exacerbations showed improvements in all parameters studied, but no statistical comparisons were performed because of their small sample size (see [Table 2](#)). AECOPD with sputum cultures isolating only common potentially pathogenic

Long-term azithromycin therapy rendered sputum cultures negative during AECOPD in nine of 20 patients during follow-up, including four from the common potentially pathogenic microorganism group, four from the *P. aeruginosa* colonization group (without any significant association with the presence of mucoid forms or inhaled colimycin therapy, data not shown), and one from the common potentially pathogenic *P. aeruginosa* group. [Table 3](#) shows the microbiological evolution of patients during azithromycin treatment in relation to sputum cultures obtained during the first year.

**Table 3**

Microbiological evolution during long-term azithromycin therapy according to baseline groups and sputum culture isolates during AECOPD

Year 1 no azithromycin	n	Year 2 azithromycin therapy				
		No AECOPD	AECOPD with negative cultures	≥1 common PPMs	AECOPD for ≥1 <i>aeruginosa</i>	AECOPD for <i>P.</i>
Common PPM	7	1	3	2	1	
<i>P. aeruginosa</i> colonization	9	2	2	0	5	
Alternating PPM	4	1	0	0	3	
Total (patients)	20	4	5	2	9	

**Abbreviations:** AECOPD, acute exacerbation of chronic obstructive pulmonary disease; PPM, potentially pathogenic microorganisms; *P. aeruginosa*, *Pseudomonas aeruginosa*.

The sensitivity of common potentially pathogenic microorganisms to macrolides before and after long-term azithromycin therapy. Interestingly, all strains of *H. influenzae* isolated were resistant to erythromycin and 30% to clarithromycin, while none were resistant to azithromycin prior to treatment. The macrolide-resistant *S. pneumoniae* strains were also resistant to clindamycin, representing a highly resistant phenotype.

**Table 4**

Common microorganisms isolated in sputum culture during exacerbations before and after starting azithromycin and its antibiogram to macrolides

Year 1 no AZT	Isolates pre-AZT	Erythromycin			Clarithromycin			Azithromycin		
		Sen	Int	Res	Sen	Int	Res	Sen	Int	Res
<i>H. influenzae</i>	10 (31.3%)	0	0	10	7	2	1	10	0	0
<i>S. pneumoniae</i>	6 (18.8%)	3	0	3	3	0	3	3	0	3
<i>M. catarrhalis</i>	15 (50%)	14	1	1	15	0	1	15	0	0
Year 2 AZT therapy	Isolates post AZT									
<i>H. influenzae</i>	1 (20%)	0	0	1	0	0	1	0	0	1
<i>S. pneumoniae</i>	4 (80%)	0	0	4	0	0	4	0	0	4
<i>M. catarrhalis</i>	0	0	0	0	0	0	0	0	0	0

**Abbreviations:** AZT, azithromycin; *H. influenzae*, *Haemophilus influenzae*; *S. pneumoniae*, *Streptococcus pneumoniae*; *M. catarrhalis*, *Moraxella catarrhalis*; SEN, sensitive; INT, intermediate; RES, resistant.

On assessment of the bactericidal effect of long-term azithromycin therapy on common potentially pathogenic microorganisms and the development of bacterial resistance, we found no isolates of *M. catarrhalis* with azithromycin resistance during follow-up, a single isolate of *H. influenzae* with resistance to the antibiotic, and four isolates of *S. pneumoniae*, all resistant to azithromycin. The prevalence of resistance did not show statistically significant differences from the figures found in the first year of the study.

## DISCUSSION

This is the first study to examine long-term intermittent azithromycin therapy over a 12-month period in patients with severe COPD and repeated AECOPD, or chronically colonized by *P. aeruginosa*, assessing its usefulness in reducing exacerbation frequency and its bactericidal effect, and comparing the results of sputum cultures at exacerbation with the prevalence of bacteria-related exacerbation before the treatment. Our results show that long-term intermittent dosing of azithromycin as add-on therapy to conventional maximum triple therapy (longacting anticholinergics, long-term beta-agonists, and inhaled corticosteroids) reduces the number of AECOPD and hospitalizations by more than a half, and also the days of hospital stay. The treatment was well tolerated over the 12-month period, and was stopped by only one patient due to dyspnea.

Few studies focusing on the prophylactic use of antibiotics in COPD to prevent AECOPD have been published thus far, most of them examining long-term use of fluoroquinolones or macrolides. Sethi et al demonstrated that a 12-month regime with pulsed moxifloxacin 400 mg once a day for 5 days every 8 weeks achieved a 25% reduction in AECOPD, and a larger reduction (45%) in patients who reported mucopurulent sputum at baseline. The authors concluded that pulsed moxifloxacin might be indicated in COPD patients with a high frequency of AECOPD, but excluded patients colonized by *P. aeruginosa*, one of the specific subgroups discussed in our study, because of the risk of development of resistant strains. Long-term macrolide therapy in COPD was also advocated in two published studies which analyzed erythromycin over a period of 12 months, with a significant reduction in the number and severity of AECOPD. In the first, Suzuki et al reported the results of a prospective randomized trial of erythromycin therapy 200–400 mg/day versus nonactive treatment for 12 months in 109 COPD patients (average FEV<sub>1</sub> 1.4 L). They found a statistically significant increase in the relative risk of AECOPD in the control group versus the erythromycin group of 4.71 (95% CI, 1.53–14.5;  $P = 0.007$ ) and more severe AECOPD in the control group than in the erythromycin group ( $P = 0.0007$ ). In the second, a single-center, randomized, controlled trial, Seemungal et al administered erythromycin 250 mg twice daily or placebo for 1 year to 109 patients with moderate to severe COPD (mean FEV<sub>1</sub> 50% of predicted). Erythromycin reduced AECOPD in relative terms by 35% and increased the median time to first exacerbation from 89 to 271 days, both differences being statistically significant.

Preliminary data from the prospective, placebo-controlled MACRO study in 1142 COPD patients randomized to receive azithromycin 250 mg or placebo daily for 1 year have been promising. Inclusion criteria were use of supplemental oxygen or

treatment with systemic steroids for an AECOPD within the previous year. The frequency of AECOPD for those receiving azithromycin was lower at 1.4 versus 1.8 patients/year ( $P = 0.004$ ).

The microbiology data collected from the MACRO study have not yet been formally published.

Neither study assessed the impact of treatment in patients colonized by *P. aeruginosa*. Seemungal et al included patients with moderate to severe COPD in their series, of whom only 35% had three or more AECOPD during the year prior to inclusion. In the MACRO study, the frequency of AECOPD was also low. Our study enrolled an homogeneous population sample of severe or very severe COPD with very frequent AECOPD and patients with chronic colonization by *P. aeruginosa*.

Azithromycin offers clinical advantages over erythromycin. Its metabolism does not interfere with the metabolic pathway of cytochrome P450, thus avoiding possible metabolic interference with other drugs often used in COPD which share the same pathway, such as steroids and theophylline. It has better gastrointestinal tolerance and less hepatotoxicity, and because it is not associated with long QT syndrome, is better tolerated and has a better safety profile in long-term use. Even though macrolides provide adequate coverage for the most frequent potentially pathogenic microorganisms identified in AECOPD, their activity against *H. influenzae* differs. Azithromycin, the prototypical 15-member ring macrolide, has greater bacteriological and clinical activity than 14-membered ring macrolides, such as erythromycin and clarithromycin. Interestingly, in our study, all strains of *H. influenzae* isolated prior to the initiation of long-term azithromycin were resistant to erythromycin and 30% were resistant to clarithromycin, while none was resistant to azithromycin.

The subanalysis shows that Group 1, despite being the one with the highest number of AECOPD and hospitalizations prior to azithromycin therapy, demonstrated the greatest improvement with long-term azithromycin treatment, with highly significant reductions of around 70% in AECOPD and hospitalizations. The mechanism of improvement may be related to the antibacterial activity of azithromycin, particularly with regard to *H. influenzae* and *M. catarrhalis*. AECOPD with isolates positive for these potentially pathogenic microorganisms fell from 25 pre-azithromycin to just one (for *H. influenzae*) during long-term azithromycin therapy. However, we did not observe this level of bacterial eradication for *S. pneumoniae*, which has a higher prevalence of resistance to azithromycin, independently of the use of this antibiotic in the study.

We cannot exclude the possibility that the improvement observed may be due in part to the anti-inflammatory and immunomodulatory properties of azithromycin. Azithromycin may decrease sputum volume and its viscoelasticity, and increase mucociliary transport. Azithromycin also accumulates in neutrophils, interfering with chemotaxis to the inflammatory focus and promoting neutrophil apoptosis and clearance by macrophages. In their trial with long-term erythromycin, Seemungal et al analyzed inflammatory mediators in sputum (interleukin-6, interleukin-8, myeloperoxidase) and plasma (interleukin-6, interleukin-8, C-reactive protein) as secondary outcomes, but found no statistically significant treatment-related differences. The lack of effect of erythromycin on inflammatory markers suggests that the antimicrobial effects of macrolides in the treatment of COPD patients may be more important.

Patients with advanced COPD, especially those with repeated courses of antibiotic therapy or oral corticosteroids and requiring hospital admissions, have an increased risk of exacerbations caused by *P. aeruginosa*. In these patients, antibiotic treatment decisions should consider both the severity of AECOPD and the risk for isolation of *P. aeruginosa*.

The fact that 45% of our patients had chronic bronchial colonization by *P. aeruginosa* (Group 2) reflects the severity of their COPD. In these patients, long-term azithromycin therapy also improved all the outcomes analyzed, achieving a statistically significant reduction of 43% in AECOPD. Hospitalizations and days of hospital stay also fell to 47% and 32%, respectively, in these patients, although these differences did not reach statistical significance.

Macrolides, especially azithromycin, are useful in the treatment of chronic bronchial colonization by *P. aeruginosa* in patients with bronchiectasis, mainly in cases associated with cystic fibrosis. Azithromycin interferes with production of virulence factors by *P. aeruginosa*, reduces biofilm formation by inhibiting alginate production, and decreases bacterial adherence. For these reasons, we think that long-term azithromycin is especially indicated in these patients. However, the reductions in hospitalizations and days of mean hospital stay are less evident, possibly because they often require prolonged hospitalizations for parenteral antibiotic treatment, because *P. aeruginosa* is often resistant to oral antibiotics in this clinical situation.

Potential limitations of our study are the small number of patients included and the absence of a control group. However, our findings are very promising, especially for selected patients with severe COPD at high risk of exacerbations despite conventional maximum treatment. This study may help in the design of future, randomized, controlled trials including more patients and assessing

the impact of treatment in patients with different degrees of severity, focusing on aspects such as efficacy, safety, development of microbiological resistance, or economic burden.

In conclusion, we have shown that long-term intermittent azithromycin therapy, administered three times a week at a dosage of 500 mg, is well tolerated and associated with significant reductions in AECOPD, number of hospitalizations, and days of hospital stay in patients with severe COPD and repeated AECOPD. This improvement is especially significant in patients with AECOPD associated with common potentially pathogenic microorganisms, possibly due to the antibacterial activity of the drug, and in patients with chronic bronchial colonization by *P. aeruginosa* due to its ability to prevent AECOPD for common potentially pathogenic microorganisms also in these patients.

## CONCLUSION

This study shows long-term intermittent azithromycin therapy may be useful in the treatment of patients with severe COPD and frequent exacerbations

## RECOMMENDATION

The study should be done among more no. of patients at different settings to identify the trend of disease in various population.

## ACKNOWLEDGMENT

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