



Does Smoking Status Modify the Efficacy of Azithromycin Prophylaxis in COPD? A Systematic Review

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ARTICLE INFO	ABSTRACT
Published Online: 19 October 2026	Introduction: Chronic obstructive pulmonary disease (COPD) is characterized by recurrent exacerbations that significantly contribute to morbidity and healthcare burden. Long-term azithromycin prophylaxis has been shown to reduce exacerbations; however, its efficacy may vary depending on patient characteristics, particularly smoking status. Objective: To assess whether smoking status modifies the efficacy of long-term azithromycin therapy for exacerbation prevention in adults with COPD. Methods: A systematic review was conducted following PRISMA guidelines. Literature was searched in PubMed, Cochrane Library, and ScienceDirect using predefined Boolean keywords. Eligible studies included adults with COPD receiving long-term azithromycin therapy for exacerbation prevention and reporting exacerbation-related outcomes with available smoking status data. A qualitative synthesis was performed due to heterogeneity in study design and reporting. Results: Four studies were included, comprising two randomized controlled trials, one retrospective cohort, and one model-based analysis. Sample sizes ranged from 20 to 1,142 patients. Azithromycin was associated with reduced exacerbation frequency, with first exacerbation hazard ratio 0.73 (95% CI 0.63–0.84) and prolonged time to first exacerbation (266 vs 174 days) in the largest trial. Additional studies demonstrated reductions in exacerbation rates from 3.22 to 1.94 events/year and from 6.8 to 2.8 events/year. Subgroup signals indicated that treatment response varied by smoking status, with reduced benefit observed in current smokers. Model-based analysis further suggested a net clinical benefit in former smokers but not in current smokers. Discussion: The findings suggest that smoking status may modify the efficacy of azithromycin, potentially due to persistent airway inflammation and altered immune response in current smokers. Conclusion: Long-term azithromycin therapy may reduce exacerbations in selected patients with COPD, particularly those with frequent exacerbations. However, evidence that smoking status modifies treatment effectiveness remains limited, and the apparent attenuation of benefit among current smokers should be considered hypothesis-generating rather than confirmatory.
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I. INTRODUCTION

Chronic obstructive pulmonary disease (COPD) remains a major global health burden, characterized by persistent airflow limitation and recurrent episodes of acute exacerbations that significantly contribute to morbidity, mortality, and healthcare utilization. Recent epidemiological estimates indicate that COPD is among the leading causes of death worldwide, with a substantial proportion of disease burden attributable to exacerbation-related complications, including hospitalization and accelerated decline in lung function.^{1,2} These exacerbations not only worsen respiratory symptoms but also have long-term consequences on quality of

life and disease progression, making their prevention a central goal in COPD management.³

Current therapeutic strategies for COPD primarily focus on bronchodilation and anti-inflammatory control through inhaled corticosteroids, long-acting β_2 -agonists, and longacting muscarinic antagonists. Although these treatments have demonstrated efficacy in reducing exacerbation frequency, a significant subset of patients continues to experience recurrent exacerbations despite optimal inhaled therapy.^{4,5} This unmet clinical need has prompted exploration of adjunctive pharmacological approaches aimed at further reducing exacerbation risk.

Macrolide antibiotics, particularly azithromycin, have emerged as a promising preventive strategy for preventing recurrent COPD exacerbations in selected high-risk patients, due to their dual antimicrobial and immunomodulatory properties. Beyond their antibacterial activity, macrolides exert anti-inflammatory effects by modulating cytokine production, reducing neutrophilic inflammation, and altering airway microbiota composition.^{6,7} Several clinical trials have demonstrated that long-term azithromycin therapy can reduce the frequency of exacerbations and improve patient-reported outcomes in individuals with COPD, especially those with frequent exacerbations.^{7,8} However, concerns regarding adverse effects, including hearing impairment and antimicrobial resistance, have limited the widespread adoption of this strategy and highlight the importance of identifying patient subgroups most likely to benefit.⁹

One potential factor influencing the efficacy of azithromycin prophylaxis is smoking status. Cigarette smoking plays a central role in the pathogenesis of COPD and is known to perpetuate airway inflammation, impair immune responses, and alter the respiratory microbiome. These mechanisms may theoretically attenuate the immunomodulatory effects of macrolide therapy, thereby influencing treatment response.^{3,6} Furthermore, previous studies have suggested that clinical outcomes and disease progression differ between current and former smokers, raising the possibility that therapeutic interventions may exhibit variable efficacy across these groups.^{1,7}

Despite the biological plausibility of smoking status as a treatment-effect modifier, existing evidence remains inconsistent and has not been systematically synthesized. While large randomized trials have included both current and former smokers, subgroup analyses examining differential responses to azithromycin are limited and often underreported. Consequently, it remains unclear whether current smokers derive the same clinical benefit from azithromycin prophylaxis as former smokers, or whether smoking status should be considered in guiding treatment decisions.

Therefore, this systematic review aimed to assess whether smoking status modifies the effectiveness of long-term azithromycin therapy for exacerbation prevention in patients with COPD, focusing on clinically relevant outcomes including exacerbation rate, time to first exacerbation, and hospitalization. By synthesizing available evidence, this study seeks to clarify whether smoking status modifies treatment response and to inform more personalized approaches to COPD management.

II. METHOD

Study Design and Reporting Guidelines

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) guidelines. The objective was to evaluate the impact of smoking status on the efficacy of azithromycin prophylaxis in patients with chronic obstructive pulmonary disease (COPD), focusing on exacerbation-related outcomes.

Search Strategy

A comprehensive literature search was performed across three electronic databases: PubMed, Cochrane Library, and ScienceDirect. The search strategy was developed to capture studies evaluating azithromycin use in COPD with outcomes related to exacerbations. The exact search string used in PubMed was (“chronic obstructive pulmonary disease” OR COPD) AND (azithromycin OR macrolide) AND (exacerbation OR exacerbations) AND (prevention OR prophylaxis OR maintenance OR long-term). For the Cochrane Library, the search string was (“chronic obstructive pulmonary disease” OR COPD) AND (azithromycin) AND (exacerbation OR exacerbations) AND (long-term OR maintenance OR prevention). For ScienceDirect, due to Boolean limitations, the search string used was COPD AND azithromycin AND exacerbation AND (long-term OR maintenance OR prevention). No field restrictions or filters were applied to maximize retrieval of relevant studies.

Eligibility Criteria

Studies were included if they involved adult patients diagnosed with COPD and evaluated long-term azithromycin therapy for the prevention of recurrent exacerbations. Eligible studies were required to report outcomes related to exacerbation rate, time to first exacerbation, or hospitalization. Additionally, studies had to provide data relevant to smoking status, either through subgroup analysis, baseline characteristics, or stratified reporting. Smoking status was categorized as current smoking, former smoking, or never smoking whenever these categories were reported by the primary studies. Current smokers were defined as participants who reported smoking at the time of study enrolment or baseline assessment. Former smokers were defined as participants who had previously smoked but had stopped before enrolment. Never smokers were defined as participants who had never smoked or had not reached the threshold for meaningful lifetime tobacco exposure, according to the definition used in the original study. If the primary study did not provide a clear definition, the reported classification was retained and this limitation was noted. Randomized controlled trials, cohort studies, and modelbased analyses were included. Studies were excluded if they were case reports, reviews, editorials, or if they involved inappropriate participant populations or non-relevant intervention regimens.

Study Selection

The study selection process was conducted in several stages. Initially, titles and abstracts were screened to identify potentially relevant articles. Following this, duplicate records

were identified and removed. The remaining studies underwent full-text assessment to determine eligibility based on the predefined criteria. Studies that did not meet the inclusion criteria were excluded, including those with inappropriate participant characteristics or intervention regimens. The final set of included studies was determined after this full-text evaluation process.

Data Extraction

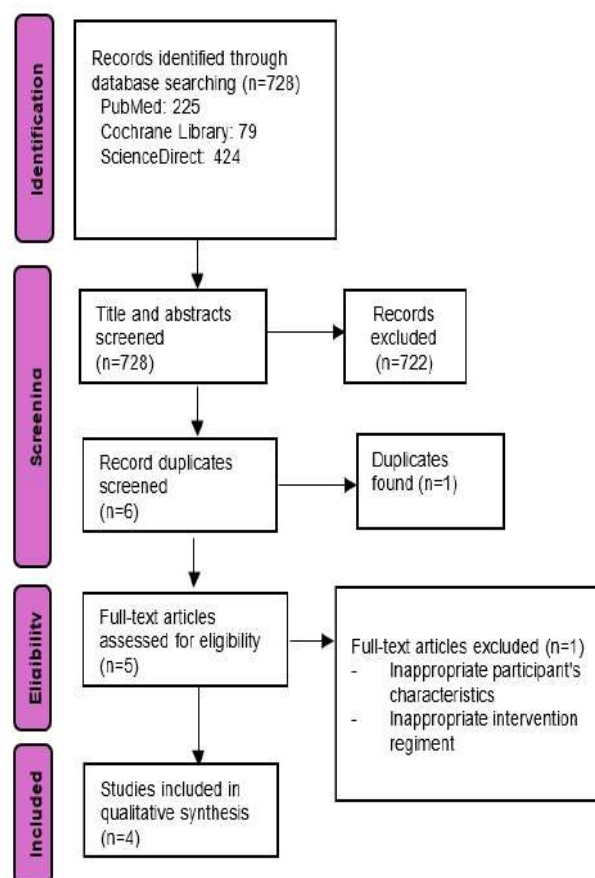
Data extraction was performed using a standardized data collection table. Extracted information included study characteristics such as first author, year of publication, country or setting, study design, population characteristics, sample size, mean age, sex distribution, and smoking status. Details regarding the intervention, including azithromycin dosing regimen and duration, were recorded, along with comparator groups where applicable. Outcome measures extracted included exacerbation rate, time to first exacerbation, hospitalization, and other relevant clinical outcomes. A narrative summary of findings was compiled for each study.

Risk of Bias Assessment

The risk of bias of the included studies was assessed qualitatively based on study design and methodological rigor. Randomized controlled trials were considered to have lower risk of bias due to randomization and blinding procedures, whereas observational and model-based studies were assessed with consideration of potential confounding, selection bias, and data limitations.

Data Synthesis

Due to heterogeneity in study design, outcome reporting, and the limited availability of stratified data based on smoking status, a quantitative meta-analysis was not performed. Instead, a qualitative synthesis was conducted to summarize findings across studies, with particular emphasis on the potential modifying effect of smoking status on the efficacy of azithromycin prophylaxis in patients with COPD.



Study	Population	Smoking comparator	Intervention vs status	Outcomes; follow-up	Key findings
Ahmadian et al. (2022)	Adults with moderate-severe COPD (GOLD II-IV), ≥1 exacerbation in prior year, on maximal inhaled therapy inputs) Simulated base cohort of 100; mean age ~65 y; sex not reported	Stratified ex-smokers (from MACRO subgroup data)	AZITHROMYCIN 250 mg daily (long-term) current vs no AZITHROMYCIN (standard care)	Exacerbations, severe mortality, AEs, QALYs 20-y modeled horizon	RR ~0.73 overall. Ex-smokers: QALY +25.3/100 (~99.9% probability of benefit). Current smokers: QALY -4.3/100 (~36.8%). Greatest benefit in frequent exacerbators.

Pomares et al. (2011)	Spain (singlecenter); retrospective before–after cohort RoB: Low	Severe COPD (FEV1 <50%), exacerbations/y or chronic aeruginosa colonization (completed treatment); age 70.9 ± 7.4 y; 24 M / 0 F	0% smokers or never/exsmokers) 12 mo vs 12 mo pretreatment (selfcontrol)	current AZITHROMYCIN (all 500 mg 3×/week for 12 mo vs 12 mo pretreatment (selfcontrol)	AECOPD, hospitalizations, microbiology 12 mo	AECOPD 6.8 → 2.8/y; hospital stay, hospitalizations → 1.4/y; shorter hospital stay. Strongest effect with bacterial colonization; well tolerated.
Uzun et al. (2014), COLUMBUS	Netherlands (singlecenter); doubleblind placebocontrolled RCT RoB: Low	≥3 exacerbations/y, stable disease, bronchiectasis n=92 (47 AZITHROMYCIN / 45 PL); age ~64.7 / 64.9 y; M/F 22/25 (I), 18/27 (C)	Current smokers: 43% (I) vs 20% (C)	AZITHROMYCIN 500 mg 3×/week for 12 mo vs placebo + standard care	Exacerbation rate, time to first exacerbation, hospitalization, QoL, AEs 12 mo	Exacerbation rate 1.94 vs 3.22/y (RR 0.58, p=0.001); time to first exacerbation 130 vs 59 d. No significant difference in hospitalization.
Albert et al. (2011), MACRO	USA (multicenter, 17 sites); double-blind placebocontrolled RCT RoB: Low	Age ≥40 y, packyears, high exacerbation risk (prior exacerbation or oxygen use), stable disease n=1,142 (570 AZITHROMYCIN / 572 PL); age 65 / 66 y; M/F ~229/341 (I), 227/345 (C)	≥10 Current smokers: 21% (I) vs 23% (C)	AZITHROMYCIN 250 mg daily for 12 mo vs placebo + usual care	Time to first exacerbation, QoL (SGRQ), colonization, AEs 12 mo	HR 0.73 (p<0.001); time to first exacerbation 266 vs 174 d; rate 1.48 vs 1.83/y. Improved QoL, but ↑ hearing loss and macrolide resistance.

III. RESULTS

Study Selection

The systematic search across PubMed, Cochrane Library, and ScienceDirect identified a total of 728 records, consisting of 225 from PubMed, 79 from the Cochrane Library, and 424 from ScienceDirect. After screening titles and abstracts, 722 records were excluded due to irrelevance, leaving six studies for further consideration. Duplicate assessment identified one duplicate record, resulting in five unique studies undergoing full-text evaluation. Of these, one study was excluded due to inappropriate participant characteristics and intervention regimen, yielding a final total of four studies included in the qualitative synthesis.

Study Characteristics

The four included studies comprised two randomized controlled trials, one retrospective cohort study, and one model-based benefit–harm analysis, reflecting a combination of high-level clinical evidence and supportive analytical data. The study populations generally included adult patients with moderate to severe chronic obstructive pulmonary disease, most of whom had a history of frequent exacerbations or

required long-term oxygen therapy. Sample sizes varied considerably, ranging from 20 patients in the observational cohort to 1,142 participants in the largest multicenter randomized trial.

Azithromycin was administered as a long-term therapy across all studies, although dosing regimens differed. Daily dosing of 250 mg and intermittent dosing of 500 mg three times weekly were the most frequently used approaches, with treatment durations consistently extending to approximately 12 months. Comparator groups included placebo arms in randomized trials and baseline pre-treatment periods in observational designs.

Smoking status was variably reported across studies. Current smokers comprised 21% and 23% of the azithromycin and placebo arms in MACRO, and 43% and 20% in COLUMBUS, whereas the retrospective cohort included no current smokers (all participants were never or former smokers). The model-based analysis did not enroll patients but simulated former and current smokers separately, using subgroup data from MACRO. Notably, COLUMBUS showed a reduction in exacerbations despite a higher proportion of current smokers in the azithromycin arm, although the small

sample size and baseline imbalance preclude firm conclusions. Only MACRO reported treatment effects stratified by smoking status. This variability in reporting is particularly relevant given the focus of the present review on smoking status as a potential modifier of treatment effectiveness.

Risk of Bias

Overall, the methodological quality of the included studies was considered to be low to moderate. The randomized controlled trials demonstrated strong internal validity, with appropriate randomization, blinding, and outcome assessment, although subgroup analyses related to smoking status were limited. The retrospective cohort study was inherently subject to confounding and selection bias due to its before–after design and lack of a concurrent control group. The model-based analysis relied on secondary data inputs from previously published studies, introducing potential limitations related to data assumptions and external validity. In accordance with the predefined criteria of this review, all studies were classified as having a maximum risk of bias of moderate.

Synthesis of Results

Across the included studies, long-term azithromycin therapy was consistently associated with a reduction in exacerbation frequency in patients with COPD. The largest randomized trial demonstrated a significant prolongation in the median time to first exacerbation and a lower annual exacerbation rate in the azithromycin group compared to placebo. Similarly, the COLUMBUS trial reported a substantial decrease in exacerbation rates and a longer time to first exacerbation among patients receiving azithromycin prophylaxis.

Observational evidence supported these findings, with marked reductions in exacerbation frequency, hospitalization rates, and length of hospital stay following initiation of azithromycin therapy. These benefits were particularly evident in patients with severe disease and frequent exacerbations, suggesting that this subgroup may derive the greatest clinical benefit from long-term macrolide therapy.

Despite the consistent overall efficacy signal, evidence regarding the influence of smoking status on treatment response was heterogeneous and largely indirect. Evidence for differential treatment response by smoking status was limited because the included studies rarely reported formal interaction tests. Therefore, the apparent attenuation of benefit among current smokers should be interpreted as hypothesis-generating rather than confirmatory. Subgroup analyses from randomized data suggested that the response to azithromycin may vary according to smoking status, with indications that current smokers experience a diminished therapeutic benefit compared to former smokers. This pattern was more explicitly suggested by the model-based analysis, which reported a more favorable net clinical benefit in former smokers than in current

smokers. However, the model-based analysis depends on assumptions regarding long-term risks, treatment effects, adverse events, and quality-adjusted lifeyears. Therefore, its findings should not be interpreted as direct clinical evidence that azithromycin causes harm in current smokers

Additional Outcomes

Beyond exacerbation-related outcomes, several studies evaluated secondary endpoints, including quality of life and safety. Improvements in quality of life, as measured by validated instruments such as the St. George’s Respiratory Questionnaire, were observed in patients receiving azithromycin. However, these benefits were accompanied by an increased incidence of adverse effects, most notably hearing impairment and the development of macrolideresistant organisms. Although these adverse events were generally manageable, they underscore the need for careful patient selection and monitoring during long-term azithromycin therapy.

Overall, the findings indicate that azithromycin prophylaxis provides clinically meaningful benefits in reducing exacerbations among patients with COPD, particularly in those with a history of frequent exacerbations. However, the magnitude of this benefit appears to be influenced by smoking status, with emerging evidence suggesting that current smoking may attenuate the therapeutic efficacy of azithromycin

IV. DISCUSSION

This systematic review found that long-term azithromycin therapy was generally associated with fewer COPD exacerbations and a longer time to first exacerbation in selected high-risk populations. Across randomized and observational evidence, the therapeutic benefit of azithromycin appears robust, particularly in patients with a history of frequent exacerbations. However, the present synthesis also highlights a clinically important and underexplored finding: the magnitude of benefit may not be uniform across all patients and appears to be influenced by smoking status. Emerging evidence suggests that current smokers derive less benefit from azithromycin compared to former smokers, indicating that smoking may act as a modifier of treatment response.

Interpretation of Findings

The overall efficacy of azithromycin observed in this review aligns with prior evidence demonstrating its role as an adjunctive therapy in COPD management.⁸ The reduction in exacerbation frequency is likely attributable not only to its antimicrobial effects but also to its immunomodulatory properties, including suppression of neutrophilic inflammation and modulation of airway cytokine profiles.^{6,7} These mechanisms are particularly relevant in COPD, where chronic inflammation and bacterial colonization play central roles in disease progression and exacerbation pathogenesis.³

However, the differential response observed between current and former smokers introduces an additional layer of complexity.¹⁰ Smoking is known to perpetuate oxidative stress, impair mucociliary clearance, and alter innate immune responses, all of which may counteract the anti-inflammatory and immunomodulatory effects of macrolides.^{3,7} Furthermore, continued exposure to cigarette smoke may sustain a pro-inflammatory airway environment, thereby reducing the relative contribution of azithromycin-mediated modulation.^{11,12} This is supported by subgroup signals from large randomized trials, where treatment effects appeared attenuated in current smokers, as well as model-based analyses demonstrating diminished or absent net clinical benefit in this population.

Another plausible explanation lies in smoking-induced alterations of the respiratory microbiome. Chronic smoking has been associated with increased microbial diversity and shifts toward pathogenic colonization, potentially reducing the effectiveness of macrolide-mediated microbial suppression.⁶ This microbiome instability may also contribute to increased antibiotic resistance, further limiting therapeutic efficacy in current smokers.

Comparison with Previous Studies

While previous systematic reviews have established the role of macrolides in reducing COPD exacerbations, few have specifically evaluated smoking status as a treatment-effect modifier. Most prior analyses have focused on overall efficacy without stratifying outcomes based on patient characteristics such as smoking behavior.¹³ The present review therefore extends existing knowledge by integrating subgroup signals and indirect evidence to explore this clinically relevant question.

Notably, the findings are consistent with observational and mechanistic studies suggesting that smoking influences both disease progression and treatment responsiveness in COPD.^{1,3} The observed variability in response also parallels findings in other respiratory conditions, where smoking has been shown to reduce responsiveness to anti-inflammatory therapies, including corticosteroids.⁴ Together, these observations support the concept of a more personalized approach to COPD management, where patient characteristics, including smoking status, inform therapeutic decisions.^{13,14}

Clinical Implications

The findings of this review have important implications for clinical practice. While long term azithromycin regimens remains an effective strategy for reducing exacerbations in COPD, its use should be carefully considered in the context of ongoing smoking. In current smokers, the potential benefits may be attenuated, and the risk–benefit balance may be less favorable, particularly given the known risks of longterm macrolide therapy, including hearing impairment and antimicrobial resistance.⁹ Conversely, former smokers and patients who have successfully ceased smoking may represent

a subgroup with greater potential to benefit from azithromycin prophylaxis.

These findings also reinforce the importance of smoking cessation as a cornerstone of COPD management. Beyond its direct effects on disease progression, smoking cessation may improve the overall COPD treatment response and could potentially influence the benefit–harm balance of macrolide therapy; however, direct evidence that cessation restores azithromycin responsiveness is currently insufficient. Therefore, integrating smoking cessation strategies with pharmacological management may yield synergistic benefits in reducing exacerbation risk.

Limitations

Several limitations should be acknowledged. First, the number of included studies was limited, and not all studies reported outcomes stratified by smoking status, necessitating reliance on indirect evidence in some cases. Second, heterogeneity in study design, population characteristics, and azithromycin dosing regimens limited the ability to perform quantitative synthesis. Third, most included studies did not report formal treatment-by-smoking interaction test. Consequently, the apparent difference in azithromycin response between current and former smokers cannot be considered confirmatory and should be interpreted as hypothesis-generating. Fourth, the inclusion of a modelbased analysis introduces assumptions that may affect external validity. Although the model suggested that the longterm benefit–harm balance may differ by smoking status, these findings depend on the model inputs and assumptions and should not be interpreted as direct clinical evidence of treatment harm among current smokers. Finally, residual confounding cannot be excluded, particularly in observational studies where smoking behavior may be associated with other unmeasured factors influencing outcomes.

This systematic review protocol was submitted to the International Prospective Register of Systematic Reviews (PROSPERO) before data extraction; however, no registration number was available at the time of manuscript preparation.

Future Directions

Future research should prioritize prospective studies and randomized trials specifically designed to evaluate smoking status as a treatment-effect modifier in COPD. Standardized reporting of subgroup analyses, including interaction testing, would facilitate more robust conclusions. Additionally, further investigation into the biological mechanisms underlying differential treatment response, particularly the role of the airway microbiome and immune modulation, may provide insights into optimizing patient selection for azithromycin prophylaxis.

V. CONCLUSIONS

Long-term azithromycin appears to reduce exacerbation frequency and delay the time to first exacerbation in selected adults with COPD, particularly those with frequent exacerbations despite optimized inhaled therapy. However, evidence that smoking status modifies azithromycin effectiveness remains limited and is derived largely from indirect subgroup findings and model-based analyses. Current smokers may experience a less favorable benefit–harm balance than former smokers, but this hypothesis requires confirmation in prospective studies with prespecified smoking-stratified analyses and formal treatment-by-smoking interaction testing. Until such evidence is available, smoking status should inform individualized risk assessment rather than serve as an absolute criterion for withholding azithromycin.

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