Original Article
DOI: https://doi.org/10.70749/ijbr.v3i7.2564

INDUS JOURNAL OF BIOSCIENCE RESEARCH
https://ijbr.com.pk
ISSN: 2960-2793/ 2960-2807

Comparison of Clinical Cure Rates of Doxycycline and Levofloxacin in the Treatment of Acute Exacerbations of Chronic Obstructive Pulmonary Disease

Amina Aslam[1], Javed Asghar[1], Abida Bashir[1], Sufyan Akram[1], Muhammad Irfan Jamil[2]

[1]Department of Pulmonology, Lahore General Hospital, Lahore, Punjab, Pakistan.
[2]Department of Nephrology, Lahore General Hospital, Lahore, Punjab, Pakistan.

ARTICLE INFO

Keywords: Acute Exacerbation of Chronic Obstructive Pulmonary Disease, COPD, Doxycycline, Levofloxacin, Clinical Cure, Oxygen Saturation, Randomized Controlled Trial, Ambulatory Management, Respiratory Infections, Antibiotic Therapy.

Correspondence to: Amina Aslam, Department of Pulmonology, Lahore General Hospital, Lahore, Punjab, Pakistan.
Email: mubashirm384@gmail.com

Declaration
Authors' Contribution
All authors equally contributed to the study and approved the final manuscript

Conflict of Interest: No conflict of interest.

Funding: No funding received by the authors.

Article History
Received: 07-06-2025 Revised: 06-07-2025
Accepted: 08-07- 2025 Published: 15-07-2025

ABSTRACT

Background: Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are a major cause of morbidity and health-care utilisation. Comparative evidence for commonly used oral antibiotics in ambulatory settings remains limited. This study assessed the early clinical efficacy of doxycycline versus levofloxacin in outpatient AECOPD. **Methods:** This randomized controlled trial was conducted in the Pulmonology Department of Lahore General Hospital, Lahore, over a five-month period (January–May 2025) after obtaining Institutional Review Board approval (2025/ERC/20) and completing trial registration (NCT06915688). Adults aged 40–75 years with spirometry-confirmed COPD and an acute exacerbation were enrolled and randomly assigned to receive oral doxycycline 100 mg twice daily or levofloxacin 500 mg once daily for five days. Clinical cure, requiring fulfilment of at least four of six predefined criteria, was evaluated two days after treatment. Baseline and follow-up clinical and laboratory parameters were analysed using appropriate statistical tests. **Results:** A total of 131 participants completed follow-up (62 doxycycline, 69 levofloxacin). Overall clinical cure occurred in 85.5% of the levofloxacin group versus 67.7% of the doxycycline group (χ^2=5.837, p=0.016). Restoration of oxygen saturation to 88–92% was significantly more frequent with levofloxacin (98.6% vs 87.1%; p=0.010), and follow-up SpO_2 was modestly higher (89.94±1.30% vs 89.42±1.27%; p=0.022). Reductions in temperature, respiratory rate, leukocytosis, and CRP were comparable between groups. Subgroup analyses showed greater benefit of levofloxacin in older adults, patients with COPD duration >5 years, and those with diabetes or hypertension. **Conclusion:** Levofloxacin demonstrated superior early clinical cure compared with doxycycline in ambulatory AECOPD, particularly in higher-risk phenotypes. These results support selective use of levofloxacin while balancing antimicrobial stewardship considerations.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, characterized by chronic inflammation and partially reversible airflow obstruction due to prolonged exposure to irritants, primarily tobacco smoke. COPD manifests in two primary forms: chronic bronchitis, involving persistent cough and sputum production, and emphysema, which causes progressive breathlessness from alveolar damage [1,2]. The disease's complexity is compounded by frequent acute exacerbations, which significantly impact morbidity, mortality, and healthcare costs. Acute exacerbations of COPD (AECOPD) are marked by a significant worsening of symptoms such as increased sputum volume and purulence, and escalated shortness of breath. These episodes, often triggered by tracheobronchial infections or environmental pollutants, not only accelerate disease progression but also increase the risk of death. Currently, about 30% to 50% of COPD patients experience at least one exacerbation annually, which is more prevalent during the colder months [3,4].

The etiology of AECOPD is multifactorial, with the predominant causes being respiratory infections and environmental triggers such as tobacco smoke and air pollution. Pathogens commonly isolated in these episodes include Haemophilus influenzae, Streptococcus pneumoniae, and Moraxella catarrhalis, among others [5]. While over 80% of exacerbations are managed ambulatorily, the role of antibiotics in their treatment remains debated. Current therapeutic strategies

emphasize the cessation of smoking, controlled oxygen therapy, and pharmacological management including bronchodilators, corticosteroids, and, critically, antibiotics. Antibiotics are recommended based on symptom severity, with first-line agents including amoxicillin and tetracyclines, and second-line agents like levofloxacin and moxifloxacin reserved for more severe cases. Despite guidelines, the optimal antibiotic strategy, particularly the comparative effectiveness of first versus second-line therapies, remains inadequately explored [6–8].

Anjum et al. (2019) conducted an RCT with 184 COPD patients, comparing oral doxycycline (100 mg twice daily) to levofloxacin (500 mg once daily) for five days. The study showed a male preponderance (106 males, 57.60%). Clinical cure was higher in the levofloxacin group at 91.3% (84 patients) compared to 78.3% (72 patients) in the doxycycline group, significant at p=0.014 [6]. Van Velzen et al. (2020) conducted a randomized, double-blind, placebo-controlled trial assessing doxycycline for preventing COPD exacerbations. Of the 887 recruited patients, 305 were randomized to receive either doxycycline (152 patients) or placebo (153 patients). Following the study, 257 out of 301 patients (85%) experienced a subsequent exacerbation: 131 (87%) in the doxycycline group and 126 (83%) in the placebo group [9]. Yoon et al. (2013) reported in an RCT involving patients with acute exacerbation of COPD (AECOPD) without pneumonia, randomized to receive levofloxacin 500 mg daily or cefuroxime (250 mg twice daily for mild-moderate exacerbations, 500 mg twice daily for severe). Clinical success in the levofloxacin group was 90.4%, comparable to 90.6% in the cefuroxime group, with a 95% confidence interval of -9.40 to 10.91 [10].

This study aims to directly compare the clinical cure rate of the first-line antibiotic doxycycline against the second-line antibiotic levofloxacin in treating AECOPD. This comparison is crucial in low-resource settings like Pakistan, where cost considerations significantly impact treatment choices. By establishing the relative effectiveness of these antibiotics, the study seeks to support evidence-based treatment protocols for managing COPD exacerbations.

MATERIAL & METHOD

This randomized controlled trial was conducted in the Pulmonology Department of Lahore General Hospital, Lahore, over a 5-month period (January 2025 to May 2025) following approval of the synopsis and issuance of the Institutional Review Board (IRB) ethical certificate (2025/ERC/20). Clinical trial registration was completed prior to patient enrollment (NCT06915688). A total sample of 234 participants, comprising 117 individuals in each treatment arm, was calculated using cure rates of 91.3% for levofloxacin and 78.3% for doxycycline, with a 95% confidence interval and 80% power. Participants were recruited through non-probability consecutive sampling. Adults aged 40 to 75 years of either sex, diagnosed with chronic obstructive pulmonary disease and presenting with an acute exacerbation, were considered eligible if they were able to provide informed consent and had not received antibiotic therapy for COPD exacerbation during the preceding four weeks. COPD was defined as a chronic inflammatory lung disease characterized by persistent respiratory symptoms including dyspnea, chronic cough, and sputum production, together with spirometric confirmation of airflow limitation demonstrated by a post-bronchodilator FEV1/FVC ratio of less than 0.70. A documented history of exposure to cigarette smoke, biomass fuel, or occupational pollutants was required, and alternative causes of airflow limitation such as asthma, heart failure, and other pulmonary disorders were excluded. An acute exacerbation of COPD was defined as a sustained worsening of symptoms within the preceding seven days accompanied by an elevated temperature above 100°F, an increase in sputum production, a respiratory rate exceeding 30 breaths per minute, a white cell count above 11×10^9/L, and a CRP concentration exceeding 10 ng/ml.

Eligible participants underwent detailed assessment, including demographic profiling, duration of COPD symptoms, comorbidities, and categorization of smoking status. Active smokers were defined as individuals reporting habitual tobacco use within the preceding 30 days; former smokers as those with a history of regular smoking for a minimum of six months before cessation; and non-smokers as individuals who had smoked fewer than 100 cigarettes or the equivalent in their lifetime. Baseline clinical evaluation included measurement of body temperature, respiratory rate, oxygen saturation on room air, WBC count, CRP concentration, and chest radiography to exclude pneumonia or other complications. Patients with hypersensitivity to doxycycline or levofloxacin, radiological evidence of pneumonia, concurrent treatment for another active infection, significant pulmonary pathology such as asthma, lung cancer, or tuberculosis, severe systemic comorbidities such as renal or hepatic insufficiency, and pregnant or breastfeeding women were excluded.

After informed consent and baseline assessment, participants were randomly assigned to treatment groups through a lottery method. One group received oral doxycycline 100 mg twice daily for five days, while the other group received oral levofloxacin 500 mg once daily for five days. All data were recorded on a standardized proforma. Clinical outcomes were assessed two days after completion of the antibiotic regimen. The primary outcome was the clinical cure rate, defined as the resolution of acute symptoms and normalization of relevant parameters. Clinical cure was established when at least four of the following criteria were achieved: reduction of temperature to below 99°F, a minimum 20% reduction in respiratory rate from baseline, restoration of oxygen saturation to between 88% and 92% on room air, reduction in sputum quantity as subjectively reported by the patient, normalization of total leukocyte count to ≤11 $\times 10^9$/L, and a reduction in CRP concentration to ≤10 ng/ml.

Data analysis was performed using SPSS version 26.0. Continuous variables such as age, duration of illness, respiratory rate, WBC count, CRP concentration, and oxygen saturation were expressed as mean and standard deviation, while categorical variables including gender, smoking status, and clinical cure rates were presented as frequencies and percentages. Comparisons between treatment groups were carried out using the independent samples t-test for continuous variables and the Chi-square

test or Fisher's exact test for categorical variables. To assess the influence of potential confounding factors including age, gender, smoking status, diabetes, and hypertension, post-stratification analyses using the Chi-square test were conducted for categorical outcomes. A p-value of less than 0.05 was considered statistically significant for all analyses. The study was designed to test the hypothesis that a significant difference existed in clinical cure rates between doxycycline and levofloxacin in the management of acute exacerbations of chronic obstructive pulmonary disease.

RESULTS

A total of 188 patients with acute exacerbation of chronic obstructive pulmonary disease were enrolled. Of these, 131 patients (69.7%) completed follow-up, including 62 patients in the doxycycline group and 69 patients in the levofloxacin group. The remaining 57 patients (30.3%) did not return for post-treatment assessment and were considered lost to follow-up.

A total of 131 patients were analyzed, with 62 (47.3%) receiving doxycycline and 69 (52.7%) receiving levofloxacin. Most participants were aged 61–75 years (66; 50.4%), and 110 (84.0%) were males. Active smokers were 53 (40.5%), former smokers 41 (31.3%), and non-smokers 37 (28.2%). COPD duration exceeded five years in 74 (56.5%) patients. Diabetes mellitus affected 48 (36.6%) and hypertension 37 (28.2%). Baseline characteristics, including age, were comparable between groups with no significant differences (all p > 0.05).

Table 1

Baseline Characteristics of Participants by Treatment Group (n = 131)

Variable	Doxycycline (n=62)	Levofloxacin (n=69)	χ^2 (p-value)
Age Category			0.935 (0.333)
40–60 years	28 (45.2%)	37 (53.6%)	
61–75 years	34 (54.8%)	32 (46.4%)	
Gender			0.001 (0.977)
Male	52 (83.9%)	58 (84.1%)	
Female	10 (16.1%)	11 (15.9%)	
Smoking Status			0.108 (0.947)
Active smoker	26 (41.9%)	27 (39.1%)	
Former smoker	19 (30.6%)	22 (31.9%)	
Non-smoker	17 (27.4%)	20 (29.0%)	
Duration of COPD			0.510 (0.475)
≤5 years	29 (46.8%)	28 (40.6%)	
>5 years	33 (53.2%)	41 (59.4%)	
Diabetes Mellitus			0.687 (0.407)
No	37 (59.7%)	46 (66.7%)	
Yes	25 (40.3%)	23 (33.3%)	
Hypertension			0.345 (0.557)
No	46 (74.2%)	48 (69.6%)	
Yes	16 (25.8%)	21 (30.4%)	

A total of 131 participants were analysed, including 62 treated with doxycycline and 69 with levofloxacin, with comparable baseline physiological and laboratory parameters. Mean baseline temperature, respiratory rate, oxygen saturation, white blood cell count, and C-reactive protein showed no significant differences between groups. Post-treatment evaluations demonstrated improvement in all parameters. Follow-up oxygen saturation was slightly higher in the levofloxacin group (89.94 ± 1.30%) than in the doxycycline group (89.42 ± 1.27%), representing the only significant difference (p = 0.022). All other post-treatment measures, including temperature, respiratory rate, WBC count, and CRP levels, remained statistically comparable.

Table 2

Comparison of outcomes between two treatment groups.

Variable	Baseline				Post-treatment			
	Doxy	Levo	MD (95% CI)	T test (P value)	Doxy	Levo	MD (95% CI)	T test (P value)
Temperature (°F)	100.80 ± 0.57	100.98 ± 0.59	-0.17 (-0.37 to 0.02)	0.088	98.52 ± 0.89	98.35 ± 2.00	0.163 (-0.38 to 0.71)	0.556
Respiratory Rate (breaths/min)	23.53 ± 1.52	23.48 ± 1.58	0.05 (-0.48 to 0.59)	0.843	17.65 ± 2.43	18.29 ± 2.38	-0.645 (-1.47 to 0.18)	0.128
Oxygen Saturation (%)	88.98 ± 1.91	88.91 ± 1.13	0.07(-0.46 to 0.60)	0.795	89.42 ± 1.27	89.94 ± 1.30	-0.523 (-0.97 to 0.07)	0.022*
White Blood Cell Count ($\times 10^9$/L)	14.10 ± 0.72	13.89 ± 0.72	0.2087 (-0.07 to 0.49)	0.143	10.51 ± 1.29	10.14 ± 1.79	0.36 (-0.17 to 0.913)	0.182
C-reactive Protein (ng/mL)	25.58 ± 3.01	25.68 ± 2.49	-0.10 (-1.05 to 0.84)	0.835	11.35 ± 4.57	10.91 ± 2.81	0.44 (-0.85 to 1.73)	0.501

Evaluation of individual clinical cure components showed variable responses in both groups. Temperature normalization occurred in 46 (74.2%) doxycycline-treated and 54 (78.3%) levofloxacin-treated participants (p=0.584). A ≥20% reduction in respiratory rate was seen in 46 (74.2%) versus 59 (85.5%) participants (p=0.105). Target oxygen saturation was restored in 54 (87.1%) and 68 (98.6%) participants, respectively, showing significance (p=0.010). Sputum reduction, leukocyte normalization, and CRP improvement were comparable between groups. Using the composite definition of cure, 42 (67.7%) participants receiving doxycycline and 59 (85.5%) receiving levofloxacin met the criteria, indicating a significant difference (p=0.016).

Table 3

Comparison of Clinical Cure Components Between Treatment Groups

Outcome Component	Doxycycline (n=62)	Levofloxacin (n=69)	χ^2 (p-value)
Temperature normalized (<99°F)	46 (74.2%)	54 (78.3%)	0.299 (0.584)
Respiratory rate improved (≥20% ↓)	46 (74.2%)	59 (85.5%)	2.628 (0.105)

Oxygen saturation restored (88–92%)	54 (87.1%)	68 (98.6%)	6.696 (0.010)
Sputum quantity reduced	34 (54.8%)	47 (68.1%)	2.439 (0.118)
WBC normalized (≤11 ×10^9/L)	47 (75.8%)	51 (73.9%)	0.062 (0.803)
CRP reduced (≤10 ng/mL)	30 (48.4%)	39 (56.5%)	0.867 (0.352)
Overall Clinical Cure (≥4 criteria met)	42 (67.7%)	59 (85.5%)	5.837 (0.016)

Clinical cure varied across subgroups. Among patients aged 40–60 years, cure rates were 78.6% with doxycycline and 89.2% with levofloxacin (p=0.240), while in those aged 61–75 years, levofloxacin showed significantly higher cure (81.2% vs. 58.8%; p=0.048). Male patients demonstrated a significant difference favoring levofloxacin (86.2% vs. 69.2%; p=0.031). Smoking status showed no significant associations. COPD duration >5 years strongly favored levofloxacin (75.6% vs. 39.4%; p=0.002). Diabetes and hypertension also significantly affected outcomes, with levofloxacin achieving superior cure rates in both subgroups. Overall, levofloxacin demonstrated higher cure rates in most clinical categories.

Table 4
Clinical Cure Stratified by Demographic and Clinical Variables

Variable	Category	Doxycycline n (%)	Levofloxacin n (%)	Chi-square (p-value)
Age Category	40–60 years	22 (78.6%)	33 (89.2%)	1.380 (0.240)
	61–75 years	20 (58.8%)	26 (81.2%)	3.926 (0.048)*
Gender	Male	36 (69.2%)	50 (86.2%)	4.632 (0.031)*
	Female	6 (60.0%)	9 (81.8%)	1.222 (0.269)
Smoking Status	Active smoker	14 (53.8%)	21 (77.8%)	3.382 (0.066)
	Former smoker	14 (73.7%)	19 (86.4%)	1.044 (0.307)
	Non-smoker	14 (82.4%)	19 (95.0%)	1.524 (0.217)
Duration of COPD	≤5 years	29 (100.0%)	28 (100.0%)	—
	>5 years	13 (39.4%)	31 (75.6%)	9.948 (0.002)*
Diabetes Mellitus	No	34 (91.9%)	43 (93.5%)	0.077 (0.781)
	Yes	8 (32.0%)	16 (69.6%)	6.762 (0.009)*
Hypertension	No	33 (71.7%)	41 (85.4%)	2.623 (0.105)
	Yes	9 (56.2%)	18 (85.7%)	3.997 (0.046)*

DISCUSSION

The present randomized comparison of doxycycline and levofloxacin for ambulatory acute exacerbations of chronic obstructive pulmonary disease (AECOPD) demonstrated a statistically and clinically meaningful early advantage for levofloxacin at two days after completion of a five-day course. Clinical cure occurred in 59 of 69 levofloxacin recipients (85.5%) compared with 42 of 62 doxycycline recipients (67.7%; χ^2=5.837, p=0.016), yielding an absolute difference of 17.8% and an approximate number needed to treat of six. Among individual endpoint components, restoration of oxygen saturation to the target range of 88–92% occurred significantly more often with levofloxacin (68/69, 98.6%) than doxycycline (54/62, 87.1%; χ^2=6.696, p=0.010), and follow-up SpO_2 was modestly but significantly higher in the levofloxacin group (89.94±1.30% vs 89.42±1.27%; mean difference −0.523%, 95% CI −0.970 to −0.076; p=0.022). Subgroup patterns suggested greater benefit in older adults (61–75 years: 81.2% vs 58.8%; p=0.048), those with longer COPD duration (>5 years: 75.6% vs 39.4%; p=0.002), and patients with diabetes (69.6% vs 32.0%; p=0.009) or hypertension (85.7% vs 56.2%; p=0.046), whereas differences were non-significant among younger participants, females, and smoking categories.

The direction and magnitude of benefit align with the only comparable head-to-head study identified. In hospitalised AECOPD treated for five days, Anjum et al. reported significantly higher composite cure with levofloxacin 500 mg daily than doxycycline 100 mg twice daily (91.3% vs 78.3%; p=0.014), an absolute difference of 13 percentage points similar to the present 17.8-point advantage, suggesting a consistent efficacy signal across settings [6]. Their subgroup results likewise showed greater benefit among males (84.3% vs 65.5%; p=0.026), with comparable high cure among females (100% vs 97.3%; p=0.289), a pattern mirrored in the present analysis and supporting modulation of antimicrobial efficacy by host and disease characteristics.

Trials comparing levofloxacin with β-lactams show largely equivalent short-term cure, consistent with the high cure rate observed here. Yoon et al. reported clinical success of 90.4% versus 90.6% (difference 0.75%, 95% CI −9.40 to 10.91) at 5–7 days post-therapy for levofloxacin versus cefuroxime, with numerically higher but non-significant microbiological efficacy for levofloxacin [10]. Petitpretz et al. similarly demonstrated non-inferiority between levofloxacin and cefuroxime for acute bronchitic exacerbations, with cure rates of 94.6% versus 93.8% and similar relapse intervals [11]. Observational evidence also aligns with these findings; Minov et al. observed clinical remission in 87.8% of COPD cases treated with levofloxacin, though non-randomized design limits inference [12].

In contrast, literature on doxycycline highlights early microbiological and symptomatic improvement but limited durability. Daniels et al. found higher day-10 clinical success with doxycycline versus placebo (80% vs 69%; OR 1.9, 95% CI 1.1–3.2; p=0.03) and better early bacteriological clearance, but convergence by day-30 (61% vs 53%; OR 1.3, p=0.20) and minimal CRP/FEV_1 differentials [13]. Van Velzen et al. reported reduced treatment failure at day-21 with doxycycline (16% vs 26.5%; p=0.03), driven by fewer rescue antibiotics and hospitalisations, but no differences by 84 days [3]. Longer-term outpatient doxycycline likewise demonstrated no improvement in time to next exacerbation or mortality [3]. Network analyses summarised by Zhang et al. confirmed doxycycline superiority over placebo for microbiological eradication but not for clinical cure or relapse prevention; levofloxacin similarly showed inconsistent superiority to active comparators [8].

Mechanistically, subgroup-specific levofloxacin benefit is plausible given its high epithelial lining-fluid penetration and enhanced activity against Gram-negative and β-lactamase–producing pathogens common in advanced or comorbid COPD, potentially accelerating improvements in gas exchange and ventilation–perfusion mismatch [7,14]. Doxycycline's bacteriostatic action, variable pneumococcal activity, and the anti-inflammatory effects of systemic steroids may attenuate detectable between-drug differences, particularly beyond the first week [15,16]. Greater benefit in diabetes and hypertension is biologically consistent with impaired host defence and higher bacterial burden [2,17]. The similarity in CRP and leukocyte trajectories here accords with prior trials suggesting that systemic inflammatory markers do not sensitively reflect short-window antibiotic effects in steroid-treated AECOPD [13,18].

This study had several limitations, including a reduced analysed sample due to loss to follow-up, absence of microbiological profiling, single-centre design, and lack of blinding, which may limit generalisability and introduce potential bias. Safety outcomes, relapse rates, and longer-term follow-up were not assessed, restricting interpretation to short-term effects. Strengths include randomized allocation, well-defined clinical endpoints, balanced baseline characteristics, and standardized treatment protocols allowing reliable head-to-head comparison. Future research should incorporate multicentre recruitment, microbiological confirmation, concealed allocation, extended follow-up, and phenotype-guided analyses to better define patient subgroups most likely to benefit from specific antimicrobial strategies in ambulatory AECOPD.

CONCLUSION

This randomized comparison demonstrated that levofloxacin provided a significantly higher early clinical cure rate than doxycycline in ambulatory acute exacerbations of chronic obstructive pulmonary disease. The superiority of levofloxacin was primarily driven by more rapid restoration of oxygen saturation, with additional benefits observed in older patients, individuals with long-standing COPD, and those with diabetes or hypertension. While both regimens achieved similar reductions in temperature, respiratory rate, leukocyte count, and C-reactive protein, levofloxacin consistently yielded better composite recovery. These findings support targeted use of levofloxacin in higher-risk ambulatory AECOPD while maintaining stewardship consideration for routine practice.

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