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REVIEW

Mechanisms, Efficacy, Safety, and Pharmacoeconomics of Low-Dose, Long-Term Macrolide Antibiotics in the Treatment of Chronic Obstructive Pulmonary Disease: A Review

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Abstract: Chronic Obstructive Pulmonary Disease (COPD) is usually associated with abnormal airways and/or alveoli caused by exposure to toxic particles or gases. In addition to their traditional anti-infective effects, macrolide antibiotics, when administered for long courses, may improve respiratory function, clinical outcomes, and quality of life in COPD patients, as well as reduce the frequency of acute exacerbations of COPD. For example, continuous azithromycin treatment for 1 year can reduce the annual frequency of acute exacerbations from 1.83 to 1.48 episodes, making it of great value in the treatment of COPD. However, macrolide antibiotics have potential adverse drug reactions, such as cardiotoxicity, diarrhea, and hearing impairment. Long-term use can also induce antibiotic resistance, which limits their widespread application. This article reviews the research progress on the mechanism of action, clinical efficacy, safety, and pharmacoeconomics of macrolide antibiotics in the treatment of COPD, aiming to provide a theoretical basis for optimizing individualized treatment strategies for COPD. For patients with frequent acute exacerbations or severe COPD, long-term treatment with azithromycin (500 mg, three times a week) is recommended; for patients with comorbid cardiovascular disease risks, electrocardiographic monitoring and risk assessment before treatment are suggested. Elderly patients or those on long-term medication need regular hearing tests.

Keywords: chronic obstructive pulmonary disease, macrolides, antimicrobial agents

Introduction

COPD is a heterogeneous disease characterized by chronic respiratory symptoms (dyspnea, cough, sputum production, acute exacerbations), resulting from airway (bronchitis, bronchiolitis) and/or alveolar abnormalities (emphysema), which cause persistent progressive airflow limitation. In recent years, macrolide antibiotics (MA) have demonstrated significant value in COPD treatment due to their anti-inflammatory and immunomodulatory effects. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2019 update introduced a new follow-up management pathway: for patients with acute exacerbations despite treatment with long-acting muscarinic antagonist (LAMA)/long-acting β2-agonist (LABA), if blood eosinophil (EOS) count is <100 cells/μL, roflumilast or azithromycin should be added. For those experiencing exacerbations on LAMA/LABA/inhaled corticosteroid (ICS) triple therapy, MA addition may be considered. GOLD 2020 further noted that besides antibacterial activity, MA exhibit potent anti-inflammatory and immunomodulatory effects, and long-term MA use reduces COPD exacerbations. GOLD 2022 highlighted that antibiotic therapy shortens recovery time, reduces risks of early relapse, treatment failure, and prolonged hospital stay, with a recommended duration of 5–7 days. GOLD 2023, 2024, and 2025 guidelines all specify that for patients with recurrent exacerbations

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(frequent exacerbator phenotype) despite single bronchodilator use, those with blood EOS ≥300 cells/μL should directly upgrade to triple inhalers, along with additional roflumilast (for FEV1% <50% and chronic bronchitis phenotype) and azithromycin (for former smokers).

Although the GOLD guidelines have repeatedly recommended the use of low-dose, long-term macrolide antibiotics for the treatment of patients with COPD, clinical practice in China has found that the prescription rate of such therapy remains relatively low. The proportion of eligible patients with severe COPD receiving long-term MA treatment still falls short of expectations. A foreign study also showed that although the utilization rate of MAs for COPD increased after the publication of authoritative randomized controlled trials (RCT) and guideline recommendations on MA therapy for COPD, the rates of COPD-related hospitalizations, emergency department visits, or exacerbations in outpatient settings did not decrease significantly. This may be related to the still low actual utilization rate of MA (only 3.2% of severe patients received MA in 2018) as well as poor patient compliance.[1] In addition, with the long-term use of antibiotics, drug resistance has become a growing concern. In the community population, the high incidence of MA resistance is closely associated with the use of MA.[2] Macrolide antibiotics generally have good treatment tolerability, but adverse effects such as cardiovascular toxicity, gastrointestinal reactions, and hearing impairment may still occur. Furthermore, as MA are widely used in clinical practice, their cost-effectiveness analysis (CEA) can provide evidence for medical insurance reimbursement decisions.[3] Therefore, this paper aims to systematically collate evidence on the mechanism of action, clinical efficacy, safety, and pharmacoeconomics of MA in COPD, so as to provide a more comprehensive and balanced theoretical basis for clinical decision-making and promote evidence-based individualized treatment.

Overview of MA

MA are commonly used clinical antibacterial agents, characterized by a fundamental macrolide ring structure in their molecular composition. Structural modification of MA has enhanced their acid stability, thereby improving bioavailability and prolonging the half-life in vivo. Common types of MA include: (1) 12-membered ring macrolides, such as vinamycin; (2) 14-membered ring macrolides, such as erythromycin, roxithromycin, clarithromycin; (3) 15-membered ring macrolides, such as azithromycin; (4) 16-membered ring macrolides, such as spiramycin, midecamycin. Figure 1 shows the molecular structure diagram of MA, a common therapeutic agent for COPD.

MA are broad-spectrum antibiotics, typically used to treat respiratory and soft tissue infections caused by Gram-positive bacteria (eg, *Streptococcus pneumoniae*) and *Haemophilus influenzae*. Additionally, they are effective against *Legionella pneumophila*, *mycoplasma, chlamydia*, and atypical mycobacteria.[4] These drugs exert antibacterial effects primarily by irreversibly binding to the 50S subunit of bacterial ribosomes, inhibiting protein synthesis.[5] MA also suppress the production of bacterial exotoxins, biofilms, quorum sensing molecules, and microbial adhesion factors.[6]

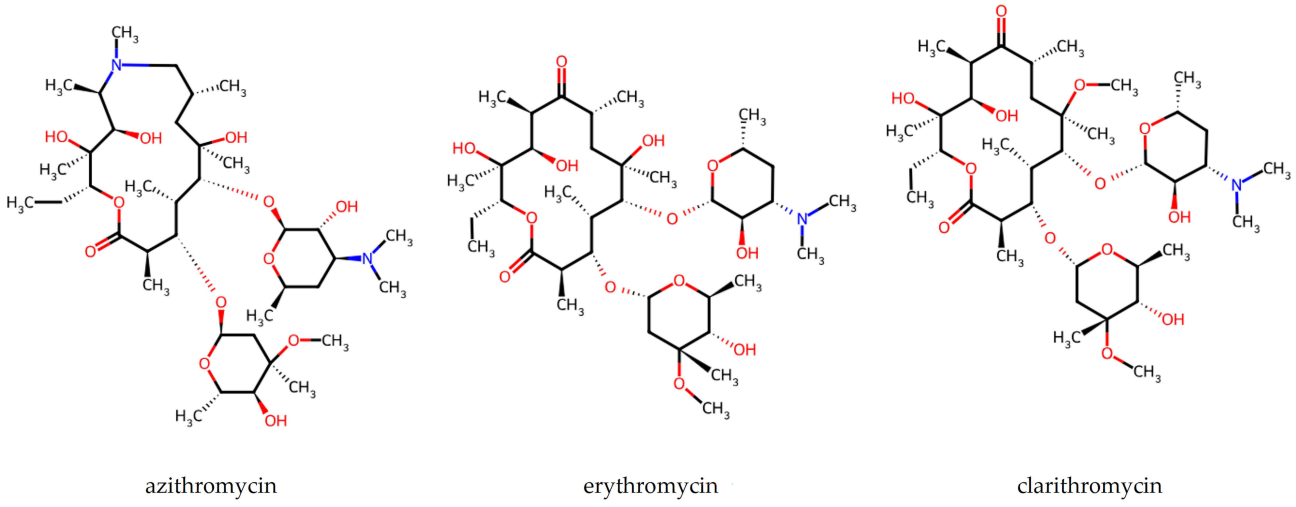

Figure 1 The molecular structure diagram of MA, a common therapeutic agent for COPD.

Beyond their broad-spectrum antibacterial activity, MA exhibit anti-inflammatory and immunomodulatory effects. MA inhibits the expression of cytokines and chemokines such as interleukin-8 (IL-8), tumor necrosis factor-α (TNF-α), adhesion molecules (integrins CD11b/CD18, L-selectin, intercellular adhesion molecule-1), and leukotriene B4 (LTB4). It also suppresses the release of proinflammatory cytokines like granulocyte colony-stimulating factor, IL-1β, and IL-10, thereby inhibiting neutrophil chemotaxis, activation, and production.[7–10] MA can also regulate the expression of co-stimulatory molecule CD80 on dendritic cells, influencing T-cell activation.[11] Recent studies have shown that MA modulate the differentiation of Th1 and Th2 cells, reestablishing Th1/Th2 balance.[12] They also regulate endothelin-1 expression/release, counteract phospholipase A2 production, and inhibit superoxide enzyme release from neutrophils and eosinophils.[6] Research indicates that MA suppress pathological mucus hypersecretion by inhibiting IL-13 and TNF-α expression/release, and possess antiviral effects, immunomodulatory antimicrobial effects, and steroid-sparing effects.[13,14]

Mechanisms of Action and Clinical Application of MA in COPD

Mechanisms of Action of MA in COPD

Chronic inflammation of the airways, lung parenchyma, and pulmonary vessels is a characteristic feature of COPD, with immune responses contributing to the amplification of this chronic inflammations.[15] The pathogenesis of COPD is extremely complex, and extensive research in recent years has unraveled significant advances in understanding its mechanisms, with recognized pathways including inflammatory responses, oxidative stress, regulation of immune imbalance, cellular senescence, genetic susceptibility, and epigenetic alterations. The following sections elaborate on the mechanisms of MA in COPD treatment from perspectives of anti-inflammation and anti-oxidation, immunomodulation, steroid resistance, and cellular senescence. Figure 2 illustrates the mechanism of action of MA in the treatment of COPD.

Anti-Inflammatory Mechanisms

Studies have shown that in a rat model of emphysema induced by cigarette smoke exposure, erythromycin intervention significantly alleviates emphysema severity and reduces the counts of neutrophils, lymphocytes, IL-8, and LTB4 in bronchoalveolar lavage fluid (BALF). Further research indicates that compared with the cigarette smoke-exposed group alone, the erythromycin intervention group exhibits decreased expression levels of lung matrix metalloproteinase-2 (MMP-2), MMP-9, and the MMP-9/tissue inhibitor of metalloproteinase-1 ratio. In-depth studies suggest that erythromycin may exert these effects via the mitogen-activated protein kinase/nuclear factor-κB (NF-κB) signaling pathway.[16] Wan et al[17] found that azithromycin improves the severity of smoking-induced emphysema in COPD rats by upregulating vascular endothelial growth factor and vascular endothelial growth factor receptor-2 expression. Jain et al[18] demonstrated that azithromycin alone or in combination with dexamethasone significantly inhibits the expression of interstitial protein markers, β-catenin, proinflammatory cytokines (TNF-α, IL-1β, IL-6), and pNF-κB in mice exposed to cigarette smoke (CS). Mechanistic studies revealed that azithromycin restores CS-induced reduction of the antioxidant transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2) and upregulates histone deacetylase 2 (HDAC2), thereby inhibiting inflammatory gene expression. Thus, its mechanisms may involve inhibiting epithelial-mesenchymal transition (EMT), reducing oxidative stress, and suppressing inflammatory responses. Qiu et al[19] showed that erythromycin activates peroxisome proliferator-activated receptor γ (PPARγ), enhancing direct interaction between PPARγ and NF-κB p65 to inhibit NF-κB p65 expression and activation, thereby reducing release of inflammatory factors IL-6 and IL-8. Erythromycin also significantly decreases reactive oxygen species (ROS) levels, alleviating oxidative stress-induced damage to PPARγ expression-findings that provide new insights for clinical COPD treatment. Li et al[20] demonstrated that erythromycin alleviates cigarette smoke extract (CSE)-induced oxidative stress in macrophages via activating the PPARγ pathway, offering a theoretical basis for antioxidant therapy in COPD. Song et al[21] used multiple in vitro (primary bronchial epithelial cells, human bronchial epithelial cells) and in vivo (SD rats and Nrf2 knockout mice) models to show that azithromycin dose-dependently restores CS-induced disruption of epithelial barrier integrity (decreased transepithelial electrical resistance [TEER] and reduced tight junction protein ZO-1 and adherens junction protein E-cadherin

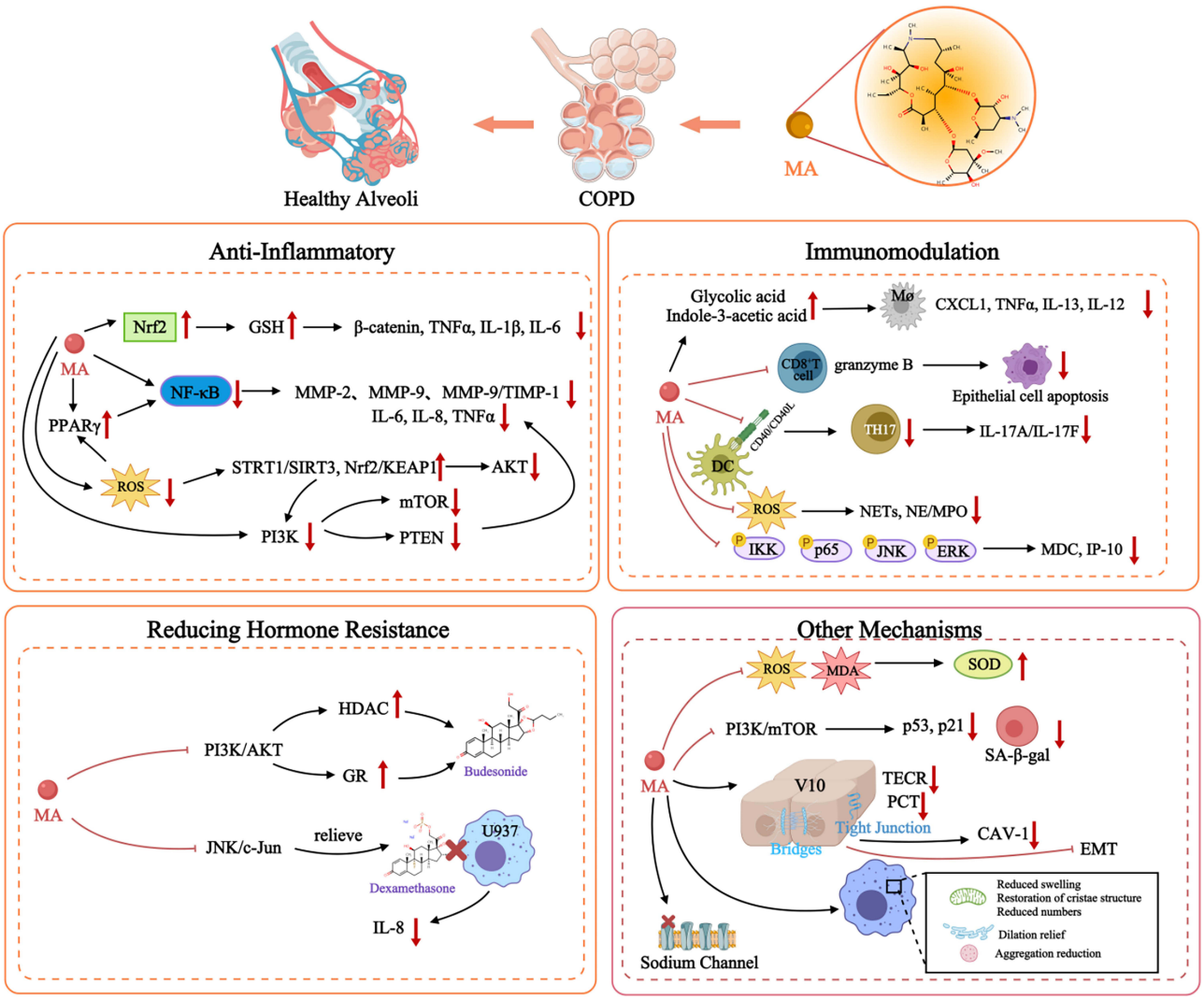

Figure 2 The mechanism of action of MA in the treatment of COPD; ↑: Indicates an upward adjustment or increase,↓: Indicates a downward adjustment or decrease.

expression), while inhibiting inflammatory factor (IL-6, TNF-α) release and cell apoptosis (Bax/Bcl-2 imbalance). Metabolomics and functional experiments further revealed that azithromycin reverses CS-mediated inhibition of Nrf2, activating the Keap1/Nrf2 pathway to significantly upregulate the glutathione (GSH) metabolic pathway, including Key enzyme activities (glutamate cysteine ligase [GCL], glutathione synthetase [GS]) and metabolite levels (L-glutamate, pyroglutamylglycine). The study also found that 14-membered ring erythromycin, similar to azithromycin, can improve the epithelial barrier through the Nrf2 pathway, while the 16-membered ring spiramycin does not have this effect, suggesting that structural characteristics are related to pharmacological effects. Ma et al[22] combined multi-omics analysis with biological experiments to show that erythromycin reduces release of inflammatory factors (IL-6, IL-8, TNF-α) by inhibiting the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT) pathway and its downstream targets (mTOR, NF-κB, PTEN). Erythromycin also decreases ROS induced by neutrophil extracellular traps (NETs), upregulates antioxidant targets (SIRT1/SIRT3, Nrf2/KEAP1), and indirectly inhibits PI3K/AKT activation-identifying new therapeutic targets for COPD and confirming that long-term low-dose erythromycin suppresses NET-related inflammation via multi-pathway coordination. Ma et al[23] found that erythromycin upregulates SIRT1 expression in human macrophage cell line U937 and lung tissues of CS-exposed mice, while decreasing NF-κB acetylation (K310) and protein levels, thereby inhibiting TNF-α and IL-6 release. Clinical studies show that erythromycin significantly reduces sputum and peripheral

blood levels of IL-17 and IL-23, associated with decreased neutrophil and increased macrophage proportions, with 12-month treatment demonstrating better efficacy than 6-month treatment.[24]

Immunomodulatory Mechanisms

Ln et al[25] demonstrated in human studies that azithromycin reduces levels of C-X-C chemokine ligand 1 (CXCL1), TNF-α, IL-13, and IL-12 in BALF, while increasing bacterial metabolites (eg, glycolic acid, indole-3-acetic acid, linoleic acid) in BALF. In vitro studies further showed that glycolic acid and indole-3-acetic acid decrease production of CXCL1, TNF-α, IL-13, and IL-12 in alveolar macrophages. Hodge et al[26] revealed in vitro that azithromycin suppresses $CD8^+$T cell granzyme B production, thereby reducing bronchial epithelial cell apoptosis and mediating immunomodulation in COPD. Liu et al[27] found that erythromycin significantly inhibits CD40 expression in CSE-exposed dendritic cells (DCs), reduces Th17 cell differentiation and related cytokine (IL-17A/IL-17F) secretion by blocking the CD40/CD40L pathway, and decreases RORγt mRNA levels. Zhang et al[28] showed that erythromycin suppresses NADPH oxidase-dependent ROS production, significantly reducing CSE-induced NETs formation and release of neutrophil elastase (NE)/myeloperoxidase (MPO). In a COPD animal model, 12-week erythromycin treatment decreased NET levels, improved emphysema, and reduced lung tissue Th1/Th17 ratios and myeloid DCs activation. Kuo et al[29] demonstrated that azithromycin selectively inhibits LPS-stimulated IκB kinase (IKK)/p65 and JNK/ERK phosphorylation in THP-1 human monocyte cells, reducing expression of Th2-related chemokine (MDC) and Th1-related chemokine (IP-10). Tang et al[30] found that erythromycin downregulates Th1/Th17 responses (decreasing IFN-γ and IL-17) and upregulates Treg cells in elastin peptide-induced emphysema mice, attenuating emphysema progression. This study identifies new immunomodulatory targets for COPD, supporting erythromycin as a potential therapy for $CD4^+$T cell-dysregulated COPD, though specific mechanisms require further investigation.

Mechanisms of Alleviating Steroid Resistance

Steroid resistance is common in COPD patients. Animal studies have shown that budesonide fails to effectively reduce serum levels of 8-epi-prostaglandin F2α (8-iso-PGF2α), IL-8, and TNF-α in COPD rats. However, compared with COPD rats treated with budesonide alone, those co-treated with erythromycin and budesonide exhibit significantly lower serum and BALF levels of 8-iso-PGF2α, IL-8, and TNF-α. Further research indicates that erythromycin enhances budesonide's anti-inflammatory activity in COPD rats by inhibiting the PI3K/AKT signaling pathway, improving HDAC2 activity.[31] Sun et al[32] also found that combined erythromycin and dexamethasone restores glucocorticoid sensitivity synergistically by inhibiting inflammatory pathways and upregulating glucocorticoid receptor (GR) expression. Multi-omics studies have shown that erythromycin restores HDAC2 and GR expression downregulated by NETs via inhibiting PI3K/AKT, thereby improving steroid resistance.[22] Kadushkin et al[33] demonstrated that combined azithromycin and budesonide more potently inhibits IL-4/8/thymic stromal lymphopoietin (TSLP) and IL-5/17A in COPD peripheral blood mononuclear cells than monotherapy, possibly by azithromycin restoring HDAC2 activity through inhibiting the PI3Kδ/Akt pathway. Bin et al[34] showed that erythromycin selectively inhibits the JNK/c-Jun pathway in CSE-exposed U937 monocyte cells, reversing dexamethasone resistance and suppressing IL-8 secretion.

Other Mechanisms of MA in COPD Treatment

Yi et al[35] established CS-induced emphysema mouse models and H_2O_2-induced premature senescence models in human bronchial epithelial cells, demonstrating that erythromycin reduces malondialdehyde and ROS levels while increasing superoxide dismutase activity under CS/H_2O_2 exposure. By inhibiting the PI3K-mTOR signaling pathway, erythromycin significantly downregulates senescence markers P53 and P21, reduces the number of β-galactosidase (SA-β-gal)-positive cells, and exerts anti-cellular senescence effects in COPD. Asbjarnarson et al[36] found that azithromycin significantly improves TEER and reduces paracellular permeability in air-liquid interface-cultured bronchial epithelial cell line VA10, outperforming clarithromycin and erythromycin. Azithromycin also induces apical localization of tight junction and desmosomal proteins, enhancing bronchial epithelial barrier integrity by downregulating caveolin-1 (CAV-1) expression and inhibiting the EMT pathway. Wang et al[37] observed via ultrastructural analysis of human macrophages that erythromycin reduces mitochondrial swelling, restores cristae structure, decreases mitochondrial number to near-normal levels, reduces lysosome aggregation, inhibits secondary lysosome formation, alleviates endoplasmic reticulum

dilation, and decreases electron-dense granules in CSE-exposed macrophages. Fujikawa et al[38] demonstrated that azithromycin improves lung function in vitro and in vivo by inhibiting epithelial sodium channel (ENaC) activity, with low-dose therapy showing clinical relevance for relieving COPD airway obstruction.

All the aforementioned basic studies have demonstrated that MA exert therapeutic effects on COPD through multi-target and multi-pathway mechanisms. The core mechanisms include inhibiting classical inflammatory pathways such as NF-κB, activating antioxidant pathways like Nrf2, regulating the balance of immune cells including Th1/Th17/Treg, restoring glucocorticoid receptor sensitivity, and counteracting oxidative stress-induced cellular senescence. Notably, MA with different structures (eg, 14-membered and 16-membered rings) may act through distinct mechanisms, suggesting a correlation between structural characteristics and pharmacological effects. These findings provide a molecular basis for understanding their diverse pharmacological actions; however, most evidence is derived from animal or cell models, and the exact mechanisms in the complex human physiological environment require further investigation. Table S1 summarizes the main mechanisms of action of MA in COPD.

Clinical Application of MA in the Treatment of COPD

Numerous studies in recent years have shown that MA exhibit promising efficacy in controlling acute exacerbations of COPD. Seemungal et al[39] early conducted a RCT of MA in COPD, administering erythromycin (250 mg twice daily) for 12 months to 53 patients and placebo to 56 controls. Results showed a significant reduction in exacerbation frequency in the erythromycin group, with no effects on FEV_1 or levels of IL-6, IL-8, and C-reactive protein in sputum and serum. Domestic study by He et al[40] randomized 31 COPD patients to 6-month erythromycin (125 mg thrice daily) or placebo, finding reduced exacerbation frequency, sputum neutrophil count, and neutrophil elastase levels in the erythromycin group. Albert et al[41] performed the largest RCT to date, enrolling 1142 COPD patients: 570 received azithromycin (250 mg daily) for 1 year, and 572 received placebo. Azithromycin prolonged time to first exacerbation (266 vs 174 days), reduced annual exacerbation frequency (1.48 vs 1.83), and improved quality of life as measured by St. George's Respiratory Questionnaire (SGRQ). Uzun et al[42] studied 92 frequent exacerbators (≥3 exacerbations in 1 year) randomized to azithromycin (500 mg thrice weekly) or placebo for 1 year, showing azithromycin significantly reduced exacerbation frequency. Recent meta-analyses confirm MA decrease annual exacerbation frequency and improve quality of life.[43] Naderi et al[44] retrospectively observed 126 severe COPD patients on azithromycin (250 mg ≥3 times/week) for ≥6 months, finding reduced exacerbation frequency, emergency visits, and hospitalizations. Pomares et al[45] followed 109 severe COPD patients on azithromycin (500 mg thrice weekly) for 2–3 years, reporting 56.2% (year 1), 70% (year 2), and 41% (year 3) reductions in exacerbations. Baalbaki et al[46] compared azithromycin (n=428) vs β-lactams (n=167) in 595 hospitalized COPD exacerbation patients, showing lower treatment failure and shorter length of stay with azithromycin. Pomares et al[47] compared low-dose (250 mg thrice weekly) vs high-dose (500 mg thrice weekly) azithromycin in 58 severe COPD patients (GOLD D), finding similar reductions in exacerbations (65.6% vs 60.5%) and hospitalizations (61.5% vs 44.8%), with no significant differences. Morasert et al[48] in Thailand found MA reduced in-hospital mortality from 14% to 8.2% in 1528 hospitalized exacerbation patients via propensity score matching. Research show MA reduce moderate-to-severe exacerbations and prolong time to first exacerbation, with limited effects in severe cases; prophylaxis increases zero-exacerbation rates in mild COPD and benefits COPD-asthma overlap by improving lung function and reducing oral steroid dependency.[49] Lam et al[50] compared roflumilast (1302 cases) vs long-term azithromycin (2573 cases) in Veterans Health Administration database, showing azithromycin conferred survival and hospitalization benefits. Yan et al[1] leveraged Ontario, Canada's health administrative data (2004–2018) to include COPD patients aged ≥65 years using long-acting inhalers. An interrupted time series compared long-term MA use trends and clinical outcomes before/after the 2011 MACRO trial (Albert et al's largest, most comprehensive RCT on MA for COPD to date). Results showed MA use increased from 0.8 to 13.8 per 1000 person-years (2004–2018), with severe COPD patients rising from 1.3 to 32.3 per 1000. Post-MACRO, annual growth rate significantly increased from 0.44 to 1.63 per 1000. Stratified analysis showed the steepest increase in severe patients, with mild patients also rising. Despite increased MA use, COPD-related hospitalizations, ED visits, or outpatient exacerbation rates did not significantly decrease, nor did adverse events. Increased MA use may relate to guideline recommendations and MACRO's influence, but real-world efficacy requires further monitoring. Cao et al[51] conducted a Meta-analysis to investigate the long-term efficacy of low-dose MA in stable

COPD. The results showed that the MA treatment group had a 23% reduction in the risk of exacerbation compared with the placebo group, and the time to first exacerbation was significantly prolonged. Subgroup analysis showed that erythromycin had a significant effect, while other drugs such as azithromycin did not show significant differences. The effect was poorer in elderly patients (>65 years old). Janjua et al[52] network meta-analysis found long-term prophylactic MA reduced exacerbations by 33% and severe adverse events by 24%, improving quality of life. Sykes et al[53] showed azithromycin benefited COPD patients with chronic cough. Cuevas et al[54] found 12-month azithromycin (250 mg thrice weekly) in 42 severe COPD reduced exacerbations by 66%, hospitalizations by 61.5%, improved PaO_2 by 9.21 mmHg, decreased serum IL-6, IL-13, TNFR2, and sputum TNFR2, reduced *Haemophilus influenzae* and *Moraxella catarrhalis*, but increased drug-resistant bacteria like *Stenotrophomonas maltophilia*. Table 1 summarizes the relevant contents of clinical studies on MA in the treatment of COPD, including researchers, study subjects, MA usage/dosage, and clinical outcomes.

In recent years, researchers have been paying increasing attention to the impact of MA on pulmonary function in the treatment of COPD. Several studies have also evaluated relevant pulmonary function parameters. For example, the study by Seemungal et al[39] found that although erythromycin treatment significantly reduced the exacerbation frequency, it did not produce a significant improvement in FEV_1. Similarly, the study by Cuevas et al[54] demonstrated that long-term MA treatment did not result in significant changes in either pulmonary function (FEV_1) or exercise tolerance (6-minute walk test, 6MWT) among patients with severe COPD. This finding may suggest that the benefits of macrolide antibiotics in COPD are derived more from their anti-inflammatory and immunomodulatory effects rather than the direct reversal of airflow limitation. Future studies are required to further clarify the impact of these agents on the long-term trajectory of pulmonary function.

In summary, numerous RCT support long-term MA therapy for reducing COPD exacerbation frequency and improving quality of life. MA also reduce exacerbations in patients with frequent exacerbations or severe COPD. Regarding the usage of MA, taking azithromycin as an example, the dosage regimen varies from once daily to three times weekly, with a single dose of 250 mg or 500 mg, administered for one year. However, the 2015 guidelines from the American College of Chest Physicians and Canadian Thoracic Society first recommended long-term MA for preventing COPD exacerbations.[55] The 2017 European Respiratory Society/American Thoracic Society guidelines and GOLD guidelines suggested adding MA to patients with moderate-to-severe airflow limitation or persistent exacerbations despite LAMA/LABA/ICS therapy.[56] The 2020 British Thoracic Society (BTS) guideline on long-term low-dose macrolides in adult respiratory diseases emphasizes their immunomodulatory (not antibacterial) effects with long-term (>6 months) use, recommending a 6–12-month trial for patients with ≥3 annual exacerbations or hospitalization history. However, more long-term (>12 months) studies are needed to assess resistance, cardiovascular risks, efficacy maintenance, and explore phenotype-specific treatment strategies.[57] Some experts argue that while long-term low-dose MA reduce exacerbation frequency, they increase bacterial macrolide resistance and mortality from respiratory diseases like pneumonia, thus discouraging their use for prophylaxis.[58] These debates highlight the need for heightened attention to the safety of MA in COPD treatment.

Adverse Reactions, Bacterial Resistance, and Effects on Normal Flora of MA in COPD Treatment

Although the therapeutic effects of MA in COPD have been confirmed, long-term low-dose use still increases adverse reactions in patients. With the widespread use of MA, bacterial resistance rates have shown an upward trend in recent years, and MA also interfere with the human normal flora.[59]

Adverse Reactions

The most common adverse reactions of MA include cardiac toxicity, such as QT interval prolongation and ventricular arrhythmia. Ray et al[60] retrospectively analyzed a Tennessee cohort (1992–2006) and found that 5-day azithromycin treatment significantly increased cardiovascular mortality compared with non-antibiotic use or other antibiotics, particularly in patients with preexisting cardiovascular diseases. Albert et al[61] argued that cardiovascular risks of MA have been

Table 1 Clinical Application of MA in the Treatment of COPD

Researcher	Research Type	Research Subjects	Number of Patients	MA Usage/Dosage	Clinical Outcomes
Seemungal et al[39]	RCT	COPD patients	53	Erythromycin (250 mg, twice daily) for 12 months	Significantly reduced frequency of acute exacerbations
He et al[40]	RCT	COPD patients	31	Erythromycin (125 mg, three times daily) for 6 months	Significantly reduced frequency of acute exacerbations, as well as reduced number of sputum neutrophils and neutrophil elastase levels
Albert et al[41]	RCT	COPD patients	570	Azithromycin (250 mg, once daily) for 1 year	Significantly prolonged time to first acute exacerbation, significantly reduced frequency of acute exacerbations within 1 year, decreased St. George's Respiratory Questionnaire (SGRQ) score, and improved quality of life
Uzun et al[42]	RCT	COPD patients with frequent acute exacerbations	92	Azithromycin (500 mg, three times a week) for 1 year	Reduced number of acute exacerbations
Naderi et al[44]	Retrospective Cohort Study	Severe COPD patients	126	Azithromycin (250 mg, at least three times a week) for 6 months	Significantly reduced number of acute exacerbations, as well as significantly decreased emergency department visits and hospitalizations
Pomares et al[45]	Retrospective Cohort Study	Severe COPD patients	109	Azithromycin (500 mg, three times a week) for 2–3 years	Reduced number of acute exacerbations by 56.2% in the first year, 70% in the second year, and 41% in the third year
Pomares et al[47]	Retrospective Cohort Study	Severe COPD patients with a history of frequent COPD acute exacerbations	58	Low-dose (250 mg/three times/week) vs high-dose (500 mg/three times/week) azithromycin for 1 year	The low-dose group had a 65.6% reduction in COPD acute exacerbations and a 61.5% reduction in hospitalizations, while the high-dose group had reductions of 60.5% and 44.8% respectively, with no significant difference between groups
Cuevas et al[54]	Retrospective Cohort Study	Severe COPD patients	42	Azithromycin (250 mg/three times/week) for 12 months	Reduced incidence of acute exacerbations by 66%, reduced hospitalization rate by 61.5%, significantly increased PaO2 by 9.21 mmHg after 12 months of treatment, and significantly decreased serum IL-6, IL-13, and TNFR2 levels
Baalbaki et al[46]	Retrospective Cohort Study	COPD patients with acute exacerbations	595	Azithromycin (250 mg/three times/week) for 12 months	Showing lower treatment failure and shorter length of stay with azithromycin
Morasert et al[48]	Retrospective Cohort Study	COPD patients with acute exacerbations	1528	NA	Reduced in-hospital mortality from 14% to 8.2%
Lam et al[50]	Retrospective Cohort Study	COPD patients	2573	NA	Azithromycin conferred survival and hospitalization benefits
Cui et al[43]	Meta-Analysis	COPD patients	2151	NA	Decrease annual exacerbation frequency and improve quality of life
Cao et al[51]	Meta-Analysis	COPD patients	2939	NA	A 23% reduction in the risk of exacerbation compared with the placebo group, and the time to first exacerbation was significantly prolonged.
Janjua et al[52]	Meta-Analysis	COPD patients	3405	NA	Reduced exacerbations by 33% and severe adverse events by 24%, improving quality of life
Sykes et al[53]	Meta-Analysis	COPD patients	275	NA	Benefited COPD patients with chronic cough
Yan et al[1]	Real-World Data Study	COPD patients	434,126	NA	Utilization rate of MA for COPD increased after the publication of authoritative RCT, the rates of COPD-related hospitalizations, emergency department visits, or exacerbations in outpatient settings did not decrease significantly

overestimated, emphasizing safety for most patients but caution in those with arrhythmias. Trac et al[62] found no increased risk of 30-day ventricular arrhythmia in elderly patients (≥65 years) on MA (azithromycin, clarithromycin, erythromycin) versus non-MA (amoxicillin, cefuroxime, levofloxacin), and MA even reduced all-cause mortality. Subgroup analysis showed no impact on arrhythmia risk in elderly patients with chronic kidney disease, heart failure, coronary artery disease, or QT-prolonging medications, with consistent mortality benefits. Mortensen et al[63] reported similar findings: azithromycin reduced 90-day all-cause mortality in elderly pneumonia patients (≥65 years) without increasing arrhythmia or heart failure, though slightly increasing myocardial infarction risk. Qiu et al[64] recommended comprehensive assessment of cardiac risk factors and baseline status before MA use, with electrocardiogram monitoring before and during treatment. Alispahic et al[65] analyzed a Danish nationwide cohort and found no increased cardiovascular risk with three MA (azithromycin, roxithromycin, clarithromycin) versus amoxicillin in COPD patients, with no differences in all-cause/cardiovascular mortality or atrial fibrillation risk. Bucci et al[66] showed that low-dose azithromycin prophylaxis (≥3 months) in COPD patients with atrial fibrillation reduced 30-day composite cardiovascular events and bleeding risk by 55% (without intracranial hemorrhage difference), with the greatest benefit within 1 week post-exacerbation. This aligns with "cardiovascular risk optimization" in atrial fibrillation management, supporting azithromycin as part of comprehensive care, though prospective validation is needed. In summary, MA demonstrate high clinical safety, but cardiac status and risk factors should be evaluated before long-term use. Other common adverse reactions include diarrhea, possibly due to prokinetic effects.[67] Cao et al[51] showed in their Meta-analysis that the incidence of gastrointestinal reactions was 5.68% in the treatment group, showing no significant difference from the placebo group (4.90%). Azithromycin may cause hearing impairment (27% vs 21%, P=0.04), but there was no significant difference in cardiovascular events. As for bacterial drug resistance, long-term use may increase the risk of drug resistance, but some studies showed that drug-resistant strains in the treatment group were instead reduced (P=0.036). Long-term low-dose MA treatment can significantly reduce COPD exacerbations, especially for high-risk patients with GOLD grade E. Hearing loss is a notable adverse effect of long-term macrolide therapy, and it has been reported with relatively high frequency particularly in azithromycin treatment. Albert et al[41] found that the incidence of hearing loss in the azithromycin group was 27%, which was significantly higher than that in the placebo group (21%), and it is age-related (the older the age, the higher the risk). Moreover, the study indicated that hearing loss usually partially or fully resolves after drug discontinuation, but advanced age, renal insufficiency, or concurrent use of other ototoxic drugs may impair such recovery. Therefore, it is recommended that hearing changes be monitored during treatment, and the necessity of drug withdrawal be evaluated when relevant symptoms occur. For the comorbidity management of COPD, when combined with type 2 diabetes mellitus, as a "corticosteroid-sparing agent", MA can reduce the dosage of corticosteroids during exacerbations, thereby improving long-term glycemic control. When combined with arrhythmia, the risk of QT interval prolongation should be alerted, and screening of electrocardiogram and drug–drug interactions is recommended before medication.[49] Table 2 summarizes the common adverse effects of MA in the treatment of COPD.

Effects on Bacterial Resistance and Normal Human Flora

Long-term MA use has raised concerns about emerging resistance and excessive suppression of normal flora.

Table 2 Common Adverse Effects of MA in the Treatment of COPD

Drug	Common Dosage and Treatment Course	Main Adverse Effects	Incidence	Outcome After Discontinuation
Azithromycin	250 mg once daily or 500 mg three times a week; treatment course ≥ 6 months	Hearing loss, gastrointestinal reactions, QT interval prolongation	Hearing loss: approximately 27% (vs placebo 21%, P=0.04); no significant difference in the incidence of gastrointestinal reactions compared with placebo; low cardiovascular risk in patients without underlying heart disease	Hearing loss usually partially or fully resolves after drug discontinuation

(*Continued*)

Table 2 (Continued).

Drug	Common Dosage and Treatment Course	Main Adverse Effects	Incidence	Outcome After Discontinuation
Erythromycin	125 mg three times a day for 6 months, or 250 mg twice a day for 12 months	Gastrointestinal discomfort, abnormal liver function	Gastrointestinal reactions are common; erythromycin is metabolized via CYP3A4, resulting in a relatively high incidence of abnormal liver function	Most cases of abnormal liver function are reversible
Clarithromycin	250–500 mg twice a day; treatment course depends on the infection	Gastrointestinal reactions, taste disturbance, abnormal liver function	Gastrointestinal reactions are common; clarithromycin therapy is often associated with taste disturbance; clarithromycin is metabolized via CYP3A4, leading to a relatively high incidence of abnormal liver function	Most adverse effects alleviate after drug discontinuation

Effects of MA on Intestinal Flora

The human intestine harbors hundreds of bacterial species in symbiotic balance, whose disruption may lead to diseases.[68] Dominant phyla include Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, and Verrucomicrobia.[69] Antibiotics can disrupt intestinal microbiota.[70] Wei et al[71] showed short-term (14-day) azithromycin reduced intestinal flora abundance/diversity in European children (predominantly Actinobacteria), while long-term (13–39 months) use had no effect. Another study found azithromycin decreased flora abundance in Indian children, primarily affecting Proteobacteria and Verrucomicrobia,[72] indicating regional and subject-dependent impacts. Intestinal flora resistance rates to erythromycin and azithromycin are 96% and 53%, respectively.[73] With the research progress in bacterial resistance mechanisms, the strategies for antibiotic use have developed rapidly. Currently, the international community universally adopts the mutant selection window (MSW) theory to optimize antibacterial strategies. MSW refers to the concentration range between the minimum inhibitory concentration (MIC) and the mutant prevention concentration (MPC), where drug-resistant mutant strains are selectively enriched and amplified. According to the MSW theory, when the antibiotic concentration is far below the MIC, it theoretically does not induce resistance and has no impact on the normal flora.[74] However, RCT on long-term low-dose MA effects on COPD patients' intestinal flora are lacking, warranting further research.

Effects of MA on Respiratory Flora

The respiratory tract harbors bacteria like *Staphylococcus aureus* (nasopharynx), *Streptococcus pneumoniae*, and *Haemophilus influenzae* (lungs). Albert et al[41] found long-term azithromycin increased upper respiratory MA-resistant bacteria in COPD patients. Pomares et al[45] showed that azithromycin treatment in severe COPD increased MA-resistant bacteria by 50%. Further analysis revealed that potential pathogens such as *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Moraxella catarrhalis* decreased by 12.5% in the first year and 17.3% in the second year, while *Pseudomonas aeruginosa* increased by 7.2% and 13.1%, respectively. Segal et al[25] observed unchanged lower airway bacterial load but reduced diversity after 8-week azithromycin, confirmed by Brill et al.[75] Overall, long-term MA decrease respiratory flora diversity and increase resistance without affecting total load, with no RCT-proven adverse outcomes. Djamin et al[76] randomized 92 frequent exacerbators to 12-month azithromycin (500 mg thrice weekly) or placebo and found baseline ermB carriage (97.7% azithromycin vs 86.1% placebo), with all samples carrying mefA. After 12 months, ermB decreased in the placebo group, while azithromycin increased relative abundance of all three resistance genes, likely due to selective pressure. The clinical benefit of azithromycin outweighed resistance risk, but continuous monitoring is needed. Carrera-Salinas et al[77] tracked 15 COPD patients on long-term azithromycin (250 mg thrice weekly) and found all pre-treatment haemophilus isolates were MA-sensitive, but resistance emerged within months via 23S rRNA mutations (eg, A2058G in ST107), ribosomal protein L4/L22 variants, or efflux pump acquisition (eg, MefE/MsrD horizontal transfer). Host adaptation involved cell wall synthesis (eg, licA, lex1), ion metabolism (eg, hgpB, hgpC), and prophage variations, highlighting the need to monitor respiratory flora for treatment failure. Novel non-antibiotic macrolides with anti-inflammatory effects (eg, EM900, CYS0073) have emerged to address resistance.[78,79]

The safety concerns of long-term MA therapy mainly focus on three aspects: cardiotoxicity, hearing impairment, and bacterial resistance. The aforementioned studies have demonstrated that with standardized patient selection and monitoring, cardiac safety is generally controllable, and there may even be cardiovascular benefits for patients with specific comorbidities. Although hearing impairment has been reported, most cases are reversible. Of greatest concern is its impact on antibiotic resistance at both the individual and population levels. While this risk does not affect clinical treatment outcomes in the short term, it requires clinicians to strictly adhere to the indications and consider the future development of macrolide drugs with anti-inflammatory and immunomodulatory properties but no antibacterial activity.

Pharmacoeconomic Studies of MA in Chronic Respiratory Inflammatory Diseases

MA have gained widespread attention for their anti-inflammatory, immunomodulatory effects, and efficacy in reducing exacerbations in COPD treatment. However, long-term use may raise concerns about resistance, adverse reactions, and increased healthcare costs. Pharmacoeconomic research quantifies MA's cost-benefit balance, providing a scientific basis for rational allocation of limited medical resources. Ahmadian et al[80] used the EPIC (A probabilistic Markov model) for a 20-year cost-effectiveness analysis of azithromycin combined with inhaled triple therapy. For patients with recent exacerbation history, azithromycin was cost-effective at willingness-to-pay thresholds of $50,000 to $100,000 per quality-adjusted life year (QALY). From a healthcare system perspective (Canada) to a societal perspective (including indirect costs), the incremental cost-effectiveness ratio (ICER) decreased by one-third. Ahmadian et al[81] further used a probabilistic Markov model to simulate 20-year COPD progression, evaluating long-term low-dose oral azithromycin for exacerbation prevention. All outcomes were weighted by health-related utilities to estimate net QALY changes, showing 17.9 net QALYs per 100 patients with exacerbation history (99.8% probability of QALY gain) and 21.8 net QALYs in frequent exacerbator subgroups (99.9% probability). O'Neill et al[82] conducted a randomized double-blind trial to assess azithromycin as add-on therapy in uncontrolled persistent asthma. The azithromycin group received 500 mg three times weekly for 48 weeks. Cost analysis from healthcare and societal perspectives showed azithromycin significantly reduced total exacerbation rate by 0.69 episodes, hospital days, and use of antibiotics/oral steroids. At a willingness-to-pay threshold of AUD 2651 per avoided exacerbation, the net monetary benefit (NMB) was AUD 2072.3, with >95% probability of cost-effectiveness (willingness-to-pay≥ AUD 100). Even doubling antimicrobial resistance (AMR) costs, NMB remained significantly positive, though AMR costs increased (AUD 172.82 vs 31.97) without statistically significant overall societal cost differences. Buendía et al[83] developed a probabilistic Markov model based on Colombia's healthcare system, simulating 5 years of standard therapy (ICS+LABA) vs standard therapy plus azithromycin for severe asthma uncontrolled by medium–high dose ICS+LABA. Azithromycin provided 0.037 QALYs per patient annually, reduced asthma exacerbation risk by 39%, and decreased 5-year total costs by USD 718 (USD 2244 vs 2961), demonstrating "absolute dominance" (lower cost, higher efficacy). Probabilistic sensitivity analysis showed 62% of simulations fell in the "low cost-high QALY" quadrant, and cost-effectiveness acceptability curves confirmed azithromycin's economic viability across all willingness-to-pay thresholds, In resource-constrained developing countries, azithromycin as an add-on therapy for severe asthma demonstrates significant cost-effectiveness, meeting the World Health Organization (WHO)-recommended willingness-to-pay threshold (three times the per capita GDP).

Pharmacoeconomic analyses have shown that in chronic respiratory diseases such as COPD and asthma, long-term low-dose azithromycin as add-on therapy not only exhibits clinical efficacy in reducing acute exacerbations but also demonstrates favorable cost-effectiveness or cost savings under various healthcare systems and economic assumptions. This holds significant implications for healthcare resource allocation decisions. However, these models typically fail to fully quantify the potential societal costs associated with long-term drug resistance. Future studies need to more comprehensively integrate the perspective of Antimicrobial Stewardship (AMS) and conduct more long-term socioeconomic evaluations. Table 3 summarizes the pharmacoeconomic studies of MA in the treatment of chronic respiratory diseases.

Table 3 Summary of Pharmacoeconomic Studies on MA in Chronic Respiratory Diseases

Disease Type	Key Findings	Pharmacoeconomic Evaluation Results	References
COPD Patients	Azithromycin combined with inhaled triple therapy is cost-effective for patients with a history of exacerbations	Meets cost-effectiveness at a willingness-to-pay (WTP) threshold of $50,000–$100,000 per QALY, with the ICER reduced by one-third	[80]
COPD Patients	Long-term low-dose azithromycin for exacerbation prevention yields significant net QALY gains in the frequent exacerbation subgroup	17.9 net QALYs gained per 100 patients with a history of exacerbations; 21.8 net QALYs in the frequent exacerbation subgroup	[81]
Asthma Patients	Azithromycin as add-on therapy reduces exacerbations and is cost-effective from both medical and societal perspectives	At a threshold of AUD 2651 per avoided exacerbation, the net monetary benefit is AUD 2072.3	[82]
Asthma Patients	Azithromycin add-on therapy demonstrates "absolute advantage" (lower cost and better efficacy) and is also cost-effective in resource-limited countries	Each patient gains 0.037 QALYs per year, with a 39% reduction in the relative risk of acute asthma exacerbations; the 5-year total cost in the azithromycin group is $718 lower than that in the standard therapy group ($2244 vs $2961)	[83]

Conclusion and Prospects

By systematically reviewing existing research findings, this study indicates that low-dose, long-term MA therapy is an effective treatment option for COPD. Its mechanisms of action are diverse, including anti-inflammation, antioxidation, immunomodulation, anti-cellular senescence, enhancement of epithelial barrier integrity, and potentiation of glucocorticoid sensitivity. Large-scale RCT, meta-analyses, and real-world data have consistently shown that MAs significantly reduce the frequency of acute exacerbations, prolong the time to the first exacerbation, and improve patients' quality of life, with overall good tolerability and rare severe adverse effects. Pharmacoeconomic analyses further support its cost-effectiveness across multiple healthcare systems. However, its side effects—such as hearing loss, diarrhea, potential cardiotoxicity, and increased bacterial resistance-cannot be ignored. Therefore, when considering long-term MA use, a comprehensive assessment of patients' underlying cardiac status and concurrent cardiac risk factors is essential; hearing changes should be monitored during treatment, and the necessity of discontinuing medication should be evaluated if symptoms occur. To address antibiotic resistance, macrolide derivatives with anti-inflammatory and immunomodulatory properties but without antibiotic effects should be developed. Treatment recommendations for COPD subgroups: For patients with frequent acute exacerbations or severe COPD, long-term azithromycin therapy (500 mg, three times a week) is recommended; for patients with comorbid cardiovascular disease risk, electrocardiography and risk assessment should be performed prior to treatment, and MA types with high cardiotoxicity should be avoided; for elderly patients, closer monitoring of hearing during treatment is required. Notably, despite proven efficacy in reducing COPD exacerbations, MA have not been included in China's COPD Diagnosis and Treatment Guidelines or primary care guidelines.

Abbreviations

MA, macrolide antibiotics; COPD, Chronic Obstructive Pulmonary Disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; LAMA, long-acting muscarinic antagonist; LABA, long-acting β2-agonist; EOS, eosinophil; ICS, inhaled corticosteroid; CEA, cost-effectiveness analysis; IL-8, interleukin-8; TNF-α, tumor necrosis factor-α; LTB4, leukotriene B4; BALF, bronchoalveolar lavage fluid; MMP, matrix metalloproteinase; NF-κB, nuclear factor-κB; CS, cigarette smoke; Nrf2, nuclear factor erythroid 2-related factor 2; HDAC2, histone deacetylase 2; EMT, epithelial-mesenchymal transition; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; CSE, cigarette smoke extract; GSH, glutathione; PI3K, phosphatidylinositol 3-kinase; AKT, protein kinase B; NETs, neutrophil extracellular traps; CXCL1, C-X-C chemokine ligand 1; DCs, dendritic cells; NE, neutrophil elastase; MPO, myeloperoxidase; IKK, IκB kinase; GR, glucocorticoid receptor; TEER, transepithelial electrical resistance; CAV-1, caveolin-1;

RCT, randomized controlled trial; SGRQ, St. George's Respiratory Questionnaire; MSW, mutant selection window; MIC, minimum inhibitory concentration; MPC, mutant prevention concentration; QALY, quality-adjusted life year; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; AMR, antimicrobial resistance.

Data Sharing Statement

No datasets were generated or analysed during the current study.

Consent for Publication

This manuscript was published with the approval of all authors, and there was no conflict of interest in the submission.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors declare that they have no competing interests.

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