

Macrolides as dual-action agents: antibacterial and immunomodulatory effects in respiratory diseases

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Abstract:

This review explores the dual role of macrolide antibiotics, focusing on their antibacterial spectrum and immunomodulatory effects, particularly in the treatment of respiratory diseases. A narrative review of the literature was performed using PubMed, ScienceDirect, Scopus, Web of Science and Google Scholar, covering English-language experimental studies, clinical trials, meta-analyses and clinical guidelines published until 2024. Macrolides, such as azithromycin, clarithromycin, and erythromycin, inhibit bacterial protein synthesis and are effective against common respiratory pathogens, including atypical organisms like *Mycoplasma pneumoniae*. The pharmacokinetics, especially azithromycin's high lung tissue concentration, support their use in conditions like community-acquired pneumonia. In addition to their antimicrobial action, macrolides exhibit significant immunomodulatory effects by reducing inflammatory cytokines, neutrophil activity, and mucus production, which is beneficial in chronic respiratory diseases such as COPD, bronchiectasis, asthma, and cystic fibrosis. Clinical studies have demonstrated that long-term macrolide therapy can decrease the frequency of exacerbations and improve quality of life in selected patients. However, concerns over antimicrobial resistance and potential side effects, including gastrointestinal issues and QT prolongation, necessitate careful patient selection and monitoring. The findings emphasize the importance of tailoring macrolide use based on local resistance patterns, disease characteristics, and individual patient profiles. This review highlights macrolides as valuable agents with both antibacterial and anti-inflammatory properties, supporting their strategic use in respiratory disease management.

Keywords: Macrolides, Azithromycin, Antibacterial, Immunomodulation, Respiratory diseases, Antimicrobial resistance

Introduction

Antibacterial agents are compounds capable of either inhibiting bacterial growth (bacteriostatic) or killing bacteria (bactericidal), while remaining safe for host tissues. Many of these agents originate from natural sources and are subsequently modified to enhance their therapeutic properties. However, the continued exposure to widespread usage and abuse of antibiotics has led to a troubling rise in bacterial resistance [1]. This resistance is commonly driven by evolutionary pressures and genetic mechanisms that allow bacteria to survive and adapt across generations, undermining the effectiveness of many conventional treatments.

Macrolides are a class of antibiotics derived from natural products, characterized by a large macrocyclic lactone ring typically containing 14, 15, or 16 members which are often linked to one or more sugar residues. These compounds exert bacteriostatic effects by reversibly binding within the nascent peptide exit tunnel of the 50S ribosomal subunit, thereby disrupting bacterial protein synthesis. Erythromycin, the earliest macrolide introduced into

clinical practice, became a vital alternative for patients allergic to penicillin or infected with penicillin-resistant organisms. Subsequent generations, including azithromycin and clarithromycin, were developed to enhance pharmacokinetics, reduce gastrointestinal side effects, and broaden antimicrobial activity to include pathogens such as *Bordetella pertussis* and *Legionella* species [2].

Beyond their antimicrobial roles, macrolides have been increasingly recognized for their anti-inflammatory effects since the 1970s. These include the suppression of pro-inflammatory cytokines, inhibition of neutrophil migration, modulation of mucus secretion, and attenuation of airway remodelling. Azithromycin has demonstrated clinical benefits in chronic inflammatory airway diseases such as asthma, cystic fibrosis, and chronic obstructive pulmonary disease. Recent studies have even suggested its ability to inhibit viral replication in alveolar epithelial cells, raising the possibility that macrolides might have been beneficial had they been discovered earlier during historical viral pandemics such as the last century's Spanish Flu [3].

Respiratory diseases, both infectious and inflammatory, remain among the leading causes of global morbidity and mortality. Recent research has underscored the critical role of immune dysregulation in exacerbating and perpetuating respiratory diseases, highlighting the complex interplay between pathogens and host immune responses. The notion that microorganisms contribute to the development and progression of chronic respiratory conditions was first introduced in the 1950s through the British hypothesis [4]. Since then, mounting evidence has affirmed that even during stable phases of diseases like chronic obstructive pulmonary disease (COPD), the presence of bacteria, viruses, and fungi within the airways is not incidental, but rather intimately linked to disease pathogenesis and clinical outcomes.

The expanding availability of advanced diagnostic tools has revolutionized our ability to detect respiratory pathogens with greater specificity and sensitivity. Molecular and metagenomic approaches have deepened our understanding of the microbial ecosystems present in both healthy and diseased lungs. These studies reveal distinct microbial patterns and offer insights into how microbial imbalance, often induced by antibiotic use, can disrupt the respiratory microbiome, a phenomenon known as lung dysbiosis [5]. Such dysbiosis can influence inflammatory pathways, compromise host defence, and impact the effectiveness of treatment strategies in chronic respiratory diseases.

This review aims to explore the dual functionality of macrolides, examining both their antimicrobial mechanisms and their capacity to modulate immune responses in the context of respiratory diseases. The review will also consider the therapeutic implications of macrolide use, including concerns over antibiotic resistance and evaluate their evolving role in the management of complex respiratory conditions.

Methodology

This study was designed as a narrative review. Relevant literature was identified through searches of the PubMed, ScienceDirect, Web of Science, Scopus and Google Scholar databases using combinations of the keywords “macrolides”, “azithromycin”, “clarithromycin”, “erythromycin”, “antibacterial”, “immunomodulation”, “respiratory diseases” and “antimicrobial resistance”. Experimental studies, randomized controlled trials, meta-analyses, systematic reviews and clinical practice guidelines published in English between 1991 and 2024 were considered.

Records were screened by title and abstract, and full texts were assessed for relevance. Studies were included if they addressed the antibacterial spectrum, pharmacokinetics, immunomodulatory mechanisms or clinical use of macrolides in acute or chronic respiratory diseases. Data on the macrolide studied, patient population or model, outcomes and adverse effects were extracted and synthesized thematically into antibacterial, immunomodulatory and clinical application sections.

Mechanism of Action and Antibacterial Spectrum of Macrolides

Macrolides stop bacterial protein synthesis by nesting deep in the nascent-peptide exit tunnel of the 50S ribosomal subunit and hydrogen-bonding to domain V of 23S rRNA, which freezes chain elongation and starves the cell of essential enzymes [6]. Because this pocket is conserved in many respiratory pathogens, drugs such as erythromycin, clarithromycin, and azithromycin remain predictably active against *Streptococcus pneumoniae*, *Moraxella catarrhalis*, and most streptococci [7]. The same ribosomal focus explains why macrolides cover “atypical” wall-less or intracellular organisms (*Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, *Legionella pneumophila*) that evade β -lactam therapy. Activity against *Haemophilus influenzae* varies as clarithromycin and its 14-hydroxy metabolite reach lower MICs than erythromycin, giving clarithromycin a clinical edge where *H. influenzae* predominates [8].

Macrolides have little effect on most Enterobacterales or *Pseudomonas* because those organisms either possess a low-affinity ribosome or pump drug out via Mef efflux channels [9]. Resistance in pneumococci is mainly driven by ermB methyl-transferase, which reshapes the ribosomal target, and mefA/E pumps. The combined prevalence now exceeds 30% in several regions, forcing guideline writers to limit macrolide monotherapy to areas where susceptibility is assured [9].

Lung-Focused Pharmacokinetics

Pharmacokinetics decide whether the in-vitro spectrum translates into clinical success. Azithromycin, an “azalide,” is acid-stable and becomes trapped in lysosomes, yielding epithelial-lining-fluid (ELF) concentrations much higher than plasma for up to seven days after a single 50 mg/kg dose [10]. Clarithromycin’s ELF levels peak lower but its active metabolite raises total anti-*Haemophilus* exposure, helping overcome intermediate resistance in vivo [10]. Even erythromycin, although unstable in stomach acid and dosed four times daily, still achieves ELF concentrations above pneumococcal MICs, explaining why it remains a viable option where cost is paramount [11].

Clinical Use in Acute Respiratory Infections

Community-acquired pneumonia (CAP)

The 2019 ATS/IDSA guideline allows azithromycin monotherapy only when local pneumococcal resistance is <25% and the patient has no major comorbidities; otherwise, it recommends a β -lactam plus macrolide to widen atypical coverage and dampen inflammation [12]. An observational cohort of 1,715 patients with a known microbial cause

showed that a β -lactam–macrolide combination was associated with lower 30-day mortality than a fluoroquinolone-based regimen, an effect most pronounced in pneumococcal CAP with a high systemic inflammatory response [13]. Randomized head-to-head data confirm that 3 days of azithromycin 500 mg once daily achieves the same 94–96% clinical cure as 10 days of clarithromycin 250 mg twice daily in mild-to-moderate CAP, validating the shorter regimen when resistance is low [14].

Pertussis and other atypical pneumonias

The CDC lists azithromycin, clarithromycin, and erythromycin as first-line agents for treatment and post-exposure prophylaxis of *Bordetella pertussis*. For infants <1 month, azithromycin is preferred because erythromycin increases the risk of hypertrophic pyloric stenosis [15]. For “walking pneumonia” due to *Mycoplasma* or *Chlamydophila*, macrolides remain the drugs of choice because β -lactams cannot reach wall-less bacteria, and tetracyclines are avoided in children [15].

Resistance-Driven Practice Changes

Global surveillance highlights a rapid rise in macrolide-resistant pneumococci, reaching >40% in parts of Latin America and Asia [9]. Because ermB-mediated methylation abolishes binding, simply raising the dose cannot restore efficacy. Many centres now abandon macrolide monotherapy for CAP when local resistance surpasses 25% and instead employ β -lactam plus doxycycline or respiratory fluoroquinolones. Stewardship programs also stress limiting macrolide prescriptions for viral upper-respiratory infections to slow resistance spread [7].

Immunomodulatory Effects of Macrolides

Macrolides such as azithromycin, clarithromycin, and erythromycin are widely used antibiotics that also show significant immunomodulatory effects. These effects are especially useful in managing chronic respiratory diseases including chronic obstructive pulmonary disease (COPD), bronchiectasis, non-eosinophilic asthma, and diffuse panbronchiolitis (DPB). These diseases are often driven by neutrophilic inflammation rather than infection. In such conditions, macrolides help reduce airway inflammation and improve patient outcomes. The macrolides are increasingly used to control disease progression and prevent flare-ups. Their ability to work on both infection and inflammation makes them a valuable therapeutic option.

Many studies have shown that macrolides help regulate the immune response in chronic lung diseases. Kanoh and Rubin [16] reported that azithromycin and clarithromycin suppress the production of cytokines like interleukin-8 (IL-8) and tumour necrosis factor- α (TNF- α), which are responsible for attracting neutrophils to the airways. Culić et al. [17] supported this finding by demonstrating that clarithromycin reduces inflammation in lipopolysaccharide-stimulated monocytes. These actions help lessen the burden of chronic airway inflammation without causing full immune suppression. Findings from both laboratory and clinical research strongly support the use of macrolides, particularly azithromycin and clarithromycin, as anti-inflammatory agents in suitable respiratory

conditions.

When comparing different macrolides, azithromycin is often preferred due to its long half-life and strong tissue penetration. Amsden [18] explained that azithromycin accumulates well in lung tissues and immune cells, allowing it to work effectively even with less frequent dosing. Clarithromycin is also beneficial, particularly in conditions such as DPB and chronic sinusitis. Shinkai et al. [19] reported that azithromycin helped improve lung function and reduce neutrophilic inflammation in transplant patients with bronchiolitis obliterans. These findings support the use of azithromycin as a preferred macrolide in long-term respiratory treatment.

Although macrolides differ in their pharmacokinetic properties, they share common mechanisms in reducing airway inflammation. Azithromycin, for example, has been shown to inhibit NF- κ B, a key transcription factor involved in activating pro-inflammatory genes. Both azithromycin and clarithromycin have been shown to reduce oxidative stress and suppress mucus production by downregulating mucin gene expression, such as MUC5AC. Furthermore, azithromycin promotes a shift in macrophage polarization toward the anti-inflammatory M2 phenotype, which supports tissue repair and resolution of inflammation. These combined actions contribute to a reduction in chronic airway inflammation and enhance long-term disease control [20].

Several clinical trials have investigated the immunomodulatory effects of macrolides, particularly in chronic respiratory diseases. These trials have provided strong evidence supporting their use in reducing airway inflammation and improving clinical outcomes. For example, a study by Sutherland et al. [21] showed that long-term azithromycin therapy reduced the frequency of exacerbations in patients with COPD and bronchiectasis, leading to improvements in lung function and overall quality of life. Additionally, clinical trials in non-eosinophilic asthma have demonstrated that macrolides like azithromycin can reduce neutrophilic inflammation, which is a primary cause of disease in these patients. These studies highlight the efficacy of macrolides beyond their antibacterial effects, offering valuable immunomodulatory benefits that help manage chronic respiratory conditions.

Clinical Applications in Respiratory Diseases

Macrolide antibiotics are well-known not only for their antibacterial activity but also for their strong immunomodulatory effects. These combined properties have made them useful in treating several chronic respiratory diseases. For some patients with long-term respiratory conditions, doctors may consider macrolide therapy, though it requires careful screening, monitoring, and patient education about the risks and benefits. The risks and benefits associated with long-term use of macrolides differ from those of shorter treatments typically prescribed in primary care settings. Before starting a long-term macrolide regimen, it is essential for patients to undergo baseline assessments, which should include an ECG and liver function tests. It is also recommended to screen for non-tuberculous mycobacterial infections in patients with COPD or bronchiectasis, and to track resistance in those with asthma. In some cases, referral to a specialist is advised, and treatment should begin only after discussing the potential advantages and disadvantages with a respiratory specialist.

Macrolides have proven effective in treating various lung diseases, with research showing that they can significantly reduce exacerbations in conditions such as COPD, asthma, bronchiectasis, and cystic fibrosis. Their effectiveness in treating infections caused by

macrolide-tolerant organisms, like *Pseudomonas aeruginosa*, supports the idea that the benefits of macrolides are not solely due to their antibacterial properties, but also their immunomodulatory effects [22]. However, inconsistent data and a limited understanding of their mechanisms of action hinder their widespread use as immunomodulatory treatments.

Cystic Fibrosis (CF) is a genetic condition that primarily impacts the airways, where bacterial infections, such as those caused by *Staphylococcus aureus* and *Pseudomonas aeruginosa*, are common [23]. Macrolides, like azithromycin and clarithromycin, are typically taken orally and have broad-spectrum activity against certain bacteria. These medications are generally well-tolerated and affordable, but their extensive use has led to the rise of bacterial resistance. Studies have explored the effects of macrolides in people with CF and chronic airway infections [23]. A review of 14 studies, mostly comparing azithromycin to a placebo, found that macrolides might improve lung function and reduce pulmonary exacerbations in CF patients. For example, a study on adults with CF chronically infected with *P. aeruginosa* showed that taking azithromycin 250 mg daily for over three months led to significant improvements in lung function (FEV1 and FVC), weight gain, and fewer courses of intravenous antibiotics compared to controls [24].

A double-blind study involving children aged six and older, with an FEV1 of 40% or higher, found long-term benefits from azithromycin given three times a week for 12 months. Azithromycin is frequently the preferred macrolide in CF patients due to its better pharmacokinetics and milder side effect profile compared to erythromycin. Some studies have shown positive efficacy and good tolerance with a three-times-a-week dose (500 mg or 250 mg for patients weighing less than 40 kg) [23]. However, larger weekly doses were linked to more gastrointestinal side effects. Previous meta-analyses, such as the one by Florescu, showed a small but notable increase in FEV1 with azithromycin compared to a placebo [23]. The Cochrane Database of Systematic Reviews has published an updated review on macrolide antibiotics for CF, and subgroup analyses often differentiate patients with and without chronic airway infections, particularly *P. aeruginosa*.

Non-Cystic Fibrosis (non-CF) Bronchiectasis is characterized by ongoing airway inflammation and dilation of the bronchial walls, which leads to excessive sputum production, frequent exacerbations, and progressive lung damage. Macrolide maintenance therapy has shown promise in treating non-CF bronchiectasis [25]. Clinical trials suggest that long-term macrolide therapy can reduce the frequency and duration of exacerbations, decrease sputum production, improve the quality of life, and slow down lung function decline [25]. A meta-analysis of 10 studies showed that macrolides significantly reduced the number of patients experiencing exacerbations, as well as the number of exacerbations per patient and hospital admissions due to exacerbations [26]. These benefits were observed in both adults and children. The study also found that only azithromycin had a significant effect in preventing exacerbations, unlike erythromycin or roxithromycin [26]. The way macrolides might reduce sputum production is thought to involve suppression of mucin synthesis. While some studies indicate that macrolides may slow lung function decline, others found no significant improvements in FEV1 or FVC [25]. The discrepancies could be due to differences in macrolide types, doses, treatment durations, and study sample sizes.

Chronic Obstructive Pulmonary Disease (COPD) is a prevalent chronic lung condition. Long-term treatment with macrolides may help some patients with COPD [27]. Macrolides, like azithromycin, have shown immunomodulatory effects in chronic inflammatory diseases, including COPD exacerbations [28]. A meta-analysis conducted in 2018 suggested that

macrolides could reduce the frequency of COPD exacerbations [28]. A 2011 randomized controlled trial further showed that daily azithromycin reduced the frequency of COPD exacerbations [28,29].

Asthma, another chronic inflammatory airway condition, may benefit from long-term macrolide treatment [27]. Macrolides are believed to have anti-inflammatory, antibacterial, and antiviral effects, which could be useful in asthma management. They are particularly recommended for non-eosinophilic asthma [28]. While some studies have suggested potential benefits in controlling asthma symptoms, results on their impact on exacerbations and asthma phenotypes have been inconsistent [30]. Long-term low-dose azithromycin therapy has shown a reduction in neutrophil extracellular traps (NETs) in asthmatic patients, particularly those with neutrophil-dominant inflammation, suggesting macrolides could be beneficial for these individuals [22]. However, no significant reduction in NETs was observed in patients with eosinophil-dominant inflammation. A randomized, double-blind, placebo-controlled trial (AMAZES study) tested azithromycin 500 mg, three times a week for 48 weeks, as an add-on therapy for adults with persistent asthma despite maintenance therapy [30]. This study reported a decrease in exacerbations and improved quality of life for patients treated with azithromycin [28]. Some studies suggest that macrolides can improve bronchial hyperresponsiveness in children [31]. Meta-analyses have also explored the long-term use of macrolides in asthma management, although macrolides are less commonly used in asthma than in CF [24].

Diffuse Panbronchiolitis (DPB) is a long-term inflammatory lung disease that affects the respiratory bronchioles. Macrolides have been effective in treating DPB. The use of erythromycin in patients with DPB significantly increased survival rates from 10–20% to over 90% [25]. Observational studies have demonstrated substantial benefits in treating DPB with erythromycin. A cohort study using erythromycin 400–600 mg daily showed a decrease in DPB symptoms, improved survival rates, and better quality of life [22].

Community-Acquired Pneumonia (CAP) is an infection acquired outside of healthcare settings. Macrolides are well-known for their antibacterial properties and are widely used to treat respiratory infections. A meta-analysis assessed the impact of adding macrolides to other antibiotics on the resolution of CAP and 30-day mortality [32]. The findings indicated that adding macrolides reduced the risk of death following CAP.

Respiratory Viral Infections (RVI) are caused by viruses that affect the nose, sinuses, throat, and lungs. Macrolides have garnered attention for their potential effectiveness in treating respiratory viral infections due to their anti-inflammatory and immunomodulatory properties. Studies have shown that macrolides are effective against rhinovirus (RV), respiratory syncytial virus (RSV), and influenza virus infections [33]. Macrolides have been found to reduce viral load and pro-inflammatory cytokines induced by these viruses. However, their anti-inflammatory effects are modest when compared to corticosteroids, and higher doses are required, questioning their use as a sole anti-inflammatory agent in viral infections [33]. The high mortality rate in respiratory viral infections is often due to an excessive inflammatory response and cytokine storms.

Chronic Rhinosinusitis (CRS) is a chronic airway disease that also affects children [31]. However, clinical evidence supporting the effectiveness of macrolides for children with CRS is limited.

Long-term, low-dose macrolides are increasingly used in pediatric chronic airway diseases.

Recent studies and guidelines support their potential benefits for children with severe asthma, CF, and non-CF bronchiectasis [31]. Azithromycin, with its long half-life and less impact on CYP3A4 enzymes, has become a focus of research in pediatrics.

Antibacterial Spectrum of Macrolides

The literature highlights how macrolides serve as frontline agents in treating acute respiratory infections, but it also reveals clinically important differences among them in terms of spectrum, pharmacokinetics, resistance vulnerability, and ideal use scenarios. By critically comparing these factors, we can make better-informed therapeutic choices and improve antibiotic stewardship in community settings.

One of the most consistent findings across studies is that azithromycin’s high tissue penetration and long epithelial-lining-fluid (ELF) half-life offer a practical advantage, allowing for short-course regimens [10]. This translates into better adherence, reduced dosing frequency, and sustained exposure against intracellular pathogens like *Mycoplasma* and *Legionella*. Studies have shown that azithromycin reaches a higher ELF/plasma ratio compared to clarithromycin and erythromycin [11]. These pharmacokinetic traits align directly with the clinical success of 3–5-day azithromycin regimens for community-acquired pneumonia (CAP) and pertussis.

Although all three macrolides share the same core mechanism, which is blocking 50S ribosomal function [6], each has different activity against *Haemophilus influenzae*, a key pathogen in bronchitis and sinusitis. Clarithromycin stands out with higher in-vitro potency, making it the preferred option in *H. influenzae*-predominant regions [8]. Meanwhile, erythromycin, though older and less tolerable, remains effective in low-resource settings due to its broad-spectrum activity and low cost.

This functional diversity is summarized in the comparison table below (Table 1). The table helps clarify why azithromycin dominates in outpatient CAP and pertussis, while clarithromycin is favoured in sinusitis, and erythromycin retains a niche in cost-sensitive contexts.

Table 1. Comparison Between Macrolides

Macrolide	Acid Stability	Tissue Penetration (ELF/Plasma Ratio)	Dosing Frequency	Coverage of <i>H. influenzae</i>	Preferred Use
Azithromycin	High	20	Once daily	Moderate	CAP, Pertussis, AECOPD
Clarithromycin	Moderate	10	Twice daily	High	Sinusitis, AECOPD
Erythromycin	Low	8	4 times daily	Low	Cost-sensitive settings

CAP guidelines from ATS/IDSA restrict azithromycin monotherapy to regions where *S. pneumoniae* macrolide resistance is below 25%, a threshold repeatedly justified by mortality and treatment failure data [7]. The presence of resistance genes like *ermB* and *mefA/E*, which prevent ribosomal binding or pump drug out, explains why dose escalation

cannot salvage treatment [9]. These observations underline that guideline shifts toward combination therapy (β -lactam + macrolide) are not just cautious—they are evidence-driven and microbiologically rational.

The literature also reflects a growing tension where macrolides are highly effective when susceptibility is preserved, but rising resistance is shrinking their utility. This is particularly evident in Latin America and parts of Asia, where resistance rates to macrolides among pneumococcal isolates exceed 40% [9]. Stewardship responses, such as shifting toward β -lactam + doxycycline or fluoroquinolone monotherapy in high-resistance areas, underscore how local resistance surveillance should shape macrolide prescribing.

Crucially, not all macrolides are interchangeable. The belief that any macrolide can substitute for another oversimplifies a nuanced therapeutic class. Azithromycin's unique pharmacokinetics and clarithromycin's superior *H. influenzae* coverage are not cross-replicable. Therefore, the decision to use a macrolide should depend not only on bacterial spectrum but also on tissue penetration, regional resistance data, and disease severity.

This review reveals that macrolides' role in acute respiratory infections is built on more than ribosomal inhibition; they offer pharmacokinetic convenience, organism-specific strengths, and proven clinical outcomes. However, preserving these benefits requires thoughtful selection based on drug properties and updated resistance data.

Immunomodulatory Effects of Macrolides

The immunomodulatory effects of macrolides represent a promising advancement in the management of chronic respiratory diseases. Unlike corticosteroids, which broadly suppress the immune system, macrolides provide a more selective anti-inflammatory approach. This targeted mechanism is particularly beneficial in conditions characterized by neutrophilic inflammation such as COPD and bronchiectasis, where corticosteroids are often less effective. In these cases, macrolides are increasingly used as additional therapy, especially for patients who continue to experience symptoms or frequent exacerbations despite standard treatment.

However, the long-term use of macrolides must be carefully considered in relation to potential risks. Studies such as those by Albert et al. [29] have linked prolonged macrolide therapy to antibiotic resistance, QT interval prolongation, and gastrointestinal side effects. Therefore, careful patient selection and regular monitoring are important, particularly for individuals who show ongoing inflammation and poor response to inhaled treatments. Overall, it is important to balance the potential benefits and risks to ensure the best outcomes.

The literature consistently supports the role of macrolides in producing significant immunomodulatory effects, especially in neutrophilic airway diseases. These effects include the suppression of key inflammatory cytokines like IL-8 and TNF- α , reduction of mucus production by regulating mucin gene expression, modulation of macrophages toward an anti-inflammatory phenotype, and inhibition of NF- κ B activity. Although these mechanisms are generally seen across different macrolides, variations in strength, distribution in the body, and duration of action influence which macrolide is most suitable for each patient, as summarized in Table 2.

Table 2. Immunomodulatory Mechanisms of Macrolides in Respiratory Disease

Mechanism	Effect	Clinical Relevance	Reference
↓ IL-8, TNF-α	Reduces cytokine-driven neutrophilic inflammation	Useful in COPD, asthma, bronchiectasis	[16,17]
↓ Neutrophil chemotaxis	Decreases airway neutrophil infiltration	Reduces mucus, improves lung function	[18,19]
↓ Mucin secretion	Suppresses MUC5AC expression in airway cells	Reduces sputum production	[16]
Macrophage modulation (M1→M2)	Promotes anti-inflammatory macrophage phenotype	Enhances resolution of airway inflammation	[18]
Inhibition of NF-κB	Downregulates multiple pro-inflammatory genes	Broad anti-inflammatory effect	[17]

Further studies have highlighted the diverse impact macrolides can have on airway epithelial biology. In a study by Tamaoki et al. [20], macrolides were shown to reduce mucus secretion by downregulating goblet cell hyperplasia, a key contributor to airway obstruction in chronic respiratory disease. Additionally, macrolides inhibit biofilm formation in pathogens such as *Pseudomonas aeruginosa*, indirectly contributing to lower inflammatory stimuli in chronic infections. These multifaceted effects underscore the utility of macrolides beyond their antibacterial roles, enabling them to serve as disease-modifying agents in chronic inflammatory lung conditions.

Another key factor is the pharmacokinetics of macrolides. Their ability to concentrate in tissues, particularly in phagocytic cells and airway linings, makes them uniquely suited for chronic therapy. For instance, azithromycin achieves high intracellular concentrations, ensuring sustained immunomodulatory effects even with intermittent dosing schedules. This ability to persist in tissues allows macrolides to maintain their therapeutic effects over extended periods, even when dosed intermittently.

From a clinical perspective, treatment duration and patient selection remain points of controversy. Although studies show benefits in patients with frequent exacerbations, guidelines vary on the appropriate duration of macrolide therapy. For example, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) suggests that long-term macrolide therapy may be beneficial for patients with frequent exacerbations despite optimal inhaled therapy. However, the risk of promoting macrolide-resistant organisms like *Streptococcus pneumoniae* and *Haemophilus influenzae* must be considered when determining the benefits of continued therapy.

Moreover, patient monitoring is crucial in mitigating potential risks. Routine ECGs to detect QT prolongation, liver function tests, and hearing assessments are recommended for patients undergoing prolonged macrolide therapy. These precautions are essential for managing rare but serious adverse effects. In the future, biomarkers or phenotypic profiling may help identify patients who are most likely to benefit from macrolide therapy, allowing for more personalized and effective treatment strategies.

Clinical Applications in Respiratory Diseases

The evidence gathered from various studies strongly supports the important role of macrolides, especially azithromycin, in treating several chronic inflammatory respiratory

diseases. A consistent finding across conditions like cystic fibrosis (CF), non-CF bronchiectasis, COPD, and severe asthma is the reduction in pulmonary flare-ups [22]. This reduction in exacerbations is a key reason for using macrolides long-term, as it has a big impact on improving patients' quality of life and decreasing the need for more intensive treatments such as intravenous antibiotics or hospital stays [24]. The data from meta-analyses, particularly for non-CF bronchiectasis, provide strong statistical evidence supporting the effectiveness of macrolides in lowering the frequency and severity of exacerbations [26].

One important point highlighted in the studies is that the effectiveness of macrolides in these conditions is mainly due to their immunomodulatory and anti-inflammatory properties, rather than just their ability to fight bacteria. This is especially apparent in conditions where bacteria alone are not the main issue, or when the pathogens involved, like *Pseudomonas aeruginosa* in CF, are resistant to macrolides [22]. These drugs are thought to help regulate the overactive inflammatory response that is common in chronic airway diseases. Research is looking into the specific ways macrolides affect neutrophil activity (for example, by reducing neutrophil extracellular traps, or NETs), cytokine production, and the formation of bacterial biofilms.

However, there are challenges and complexities that need attention. One of the biggest issues is the inconsistency of results from different studies, particularly when it comes to the effects of macrolides on lung function and symptoms in diseases like bronchiectasis and asthma [25]. This variability may be caused by differences in the type of macrolide used (azithromycin tends to show more consistent results than erythromycin or roxithromycin in some cases), as well as variations in dosing, treatment length, and patient characteristics. There is still a lot we do not know about how these medications work, which makes it harder to decide who will benefit most from treatment and how to personalize it.

The most significant drawback of long-term macrolide use is the increased risk of antimicrobial resistance [23]. This is a serious public health concern that could limit the future usefulness of these drugs for both chronic treatment and acute infections. Strategies like taking breaks from treatment (treatment holidays) are recommended to help reduce this risk [27]. In addition, macrolides, particularly when taken in high doses or frequently, can cause side effects, mainly gastrointestinal problems, and there are concerns about possible cardiac issues (such as QTc prolongation) and hearing loss. However, the risk of cardiac problems tends to be lower when adjusting for individual patient characteristics [27].

Clinical guidelines and expert advice generally suggest a careful approach. Macrolides are usually recommended as additional treatment when standard therapies have been optimized but symptoms and flare-ups continue. They are not typically the first choice for treatment [31]. It is crucial to screen patients before starting treatment and continue monitoring them for antibiotic resistance and side effects. Deciding to start long-term macrolide therapy should be a joint decision between the patient and their healthcare provider, with thorough discussions about the risks and benefits. The patient's specific characteristics, like having neutrophil-dominant inflammation in asthma or frequent exacerbations in bronchiectasis, may help identify those who are most likely to benefit from macrolide therapy [22].

There is a clear need for more research in this area. Larger and better-designed randomized controlled trials are needed to determine the best doses, treatment lengths, and specific types of macrolides for different diseases and patient groups. Research into new macrolides

that maintain immunomodulatory effects without antibacterial activity could help avoid the problem of resistance. A better understanding of the underlying mechanisms of action will also help doctors better select patients and personalize their treatments. While there is growing evidence for the use of macrolides in children, particularly for conditions like severe asthma and CF, the evidence base is not as strong as it is in adults, indicating the need for more high-quality studies focused on pediatric populations.

Overall, long-term macrolide therapy offers a valuable treatment option for certain chronic respiratory diseases, particularly for reducing flare-ups through immunomodulatory effects. However, the decision to use them must consider the serious risks of antimicrobial resistance and potential side effects. The key points are summarized in Table 3.

Table 3. Macrolide Use in Chronic Respiratory Disease

Topic	Key Points
Macrolides in Chronic Respiratory Diseases	Macrolides, especially azithromycin, help manage diseases like CF, bronchiectasis, COPD, and asthma.
Reduction in Pulmonary Flare-ups	Long-term use reduces exacerbations and hospitalizations, improving quality of life.
Immunomodulatory Effects	Macrolides mainly work due to their anti-inflammatory effects rather than just antibacterial properties.
Variability in Study Results	Results on lung function and symptoms vary due to differences in drug types, dosing, and patient factors.
Antimicrobial Resistance Risk	Increased use of macrolides leads to a higher risk of antimicrobial resistance.
Side Effects of Macrolides	Side effects include gastrointestinal issues, QTc prolongation, and hearing loss, particularly at high doses.
Clinical Guidelines for Use	Macrolides are generally used as add-on therapy after other treatments have failed, not as a first-line option.

Conclusion

Macrolides have demonstrated a unique dual function as both antibacterial and immunomodulatory agents, offering significant therapeutic advantages in the management of respiratory diseases. Their well-established antimicrobial effects, especially against common respiratory pathogens, and their ability to modulate the immune response in chronic conditions like COPD, bronchiectasis, and asthma, make them valuable tools in clinical practice. Macrolides, especially azithromycin and clarithromycin, help control chronic respiratory diseases by reducing airway inflammation and the frequency of exacerbations. Among them, azithromycin stands out due to its favourable pharmacokinetics, tissue penetration, and tolerability, which contribute to its widespread use in both acute and chronic respiratory conditions.

Despite these advantages, the growing concern of macrolide resistance presents a major challenge. Resistance driven by genetic mechanisms such as *ermB* and *mefA/E*, ribosomal methylation and efflux pumps, limits the efficacy of macrolides, which necessitates a shift toward combination therapy and stricter prescribing practices. The literature also highlights the need for cautious patient selection and ongoing monitoring when using macrolides long-

term, as extended use may lead to adverse effects including QT prolongation, gastrointestinal issues, and the potential for hearing loss. Overall, while macrolides offer promising benefits beyond their antibacterial actions, their use must be guided by evidence, resistance patterns, and individual patient needs.

Future Recommendations

Future research should focus on three key areas. Firstly, more investigation is needed to understand the potential role of macrolides in treating viral respiratory infections, especially in reducing inflammation and viral load. Secondly, additional large-scale trials are essential to evaluate the long-term safety of macrolide therapy, particularly in diverse patient populations. Finally, to preserve their effectiveness, macrolides must be integrated into antimicrobial stewardship programs to minimize resistance development and ensure their continued clinical value.

Conflict of interest

The authors declare no conflict of interest.

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