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The Value of Macrolide-Based Regimens for Community-Acquired Pneumonia

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Abstract Macrolide antimicrobials are commonly prescribed, specifically for the treatment of respiratory tract infections. Although still effective, the development of widespread macrolide resistance has limited their use. Aside from their antimicrobial effects, macrolides are also known to possess immune-modulatory properties which may confer a survival benefit in both acute and chronic inflammatory states. This review discusses the efficacy, potential mechanisms, and adverse effects of macrolide therapy specifically in community-acquired pneumonia in outpatients, hospitalized ward patients, and those requiring intensive care unit admission. Challenges for ongoing research in this field are discussed and treatment recommendations offered.

Keywords Macrolide-based regimens · Community-acquired pneumonia · Macrolide antimicrobials · Respiratory tract infections

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Introduction

Macrolides are used in clinical medicine for the treatment of a variety of infections but most commonly respiratory tract infections. Aside from their antimicrobial effects, macrolides are also known to possess immune-modulatory properties—although the clinical significance of these properties, particularly in acute infection, is largely unknown.

Given their relative safety and convenience, macrolides have been used liberally, resulting in the development of widespread antimicrobial resistance. Fortunately, North America has been less affected compared with other parts of the world. As a result, macrolides still remain an attractive option as both empiric and targeted therapies in respiratory infections.

The objective of this review is to discuss the efficacy of macrolides, specifically in community-acquired pneumonia (CAP). We will discuss outpatients, hospitalized ward patients, and those requiring intensive care unit (ICU) admission for severe CAP separately. A thorough literature review was undertaken to identify contemporary papers published in this subject area.

Mechanisms of Action and Antimicrobial Spectrum

Macrolides are bacteriostatic antimicrobials acting through interruption of bacterial protein synthesis. Macrolides reversibly bind to the 23S ribosomal RNA of the 50S bacterial ribosome subunit, inhibiting RNA-dependent protein synthesis. Peptide elongation is inhibited and incomplete peptide chains detach prematurely [1]. Unfortunately, point mutations in the 23S rRNA binding site can confer class-wide resistance [2].

Traditionally, macrolides have been used for broad Gram-positive coverage including *Streptococcus pneumoniae*, other

streptococcal species, and anaerobic Gram-positive bacteria (e.g., Prevotella, non-difficile Clostridia). Macrolides have limited Gram-negative antimicrobial effect but exhibit activity against many miscellaneous microorganisms such as mycobacteria, spirochetes, Bordetella, Coxiella, and atypicals such as *Legionella pneumophila*, Mycoplasma, and Chlamydia [3, 4]. The advanced macrolides, such as azithromycin, have extended spectra including greater Gram-negative activity against Enterobacteriaceae, *Neisseria gonorrhoeae*, and important CAP pathogens such as *Haemophilus influenzae* and *Moraxella catarrhalis* [3, 5].

Ketolides, a subclass of macrolides, bind to the ribosome with greater affinity and provide even broader antimicrobial coverage. Ketolides confer more reliable coverage of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*, as they are less vulnerable to the development of resistance [6]. Cethromycin was rejected by the FDA in 2009 based on insufficient evidence for efficacy in CAP, and potentially fatal hepatotoxicity led to a black box warning for telithromycin in 2010; however, two new ketolides are in advanced phase clinical trials [6, 7].

Antimicrobial Resistance

Macrolide resistance varies by region but has been steadily increasing worldwide, with *S. pneumoniae* resistance rates as high as 96 % in Asia [8], approximately 30–40 % in the USA [9, 10], and 16 % in Canada [11]. *Mycoplasma pneumoniae* resistance is also becoming more prevalent with resistance rates greater than 80 % in one Chinese study [12]. US estimates of macrolide resistance in *M. pneumoniae* are substantially lower—approximately 10 % [13]. Resistance rates in *H. influenzae* and *M. catarrhalis* are even lower, as US data from 2008–2010 reports 1.3 and 0.5 % resistance for each pathogen, respectively [10].

Many risk factors for *S. pneumoniae* macrolide resistance have been described. The most consistently reported are recent macrolide use as well as exposure to other classes of antibiotics [14–16]. One recent study found macrolide resistance was associated with older age, antibiotic use in the previous 30 days, and chronic obstructive pulmonary disease (COPD) [15]. Young age (less than 5 years), daycare attendance, and recurrent otitis media have been identified as risk factors in the paediatric population [17–19]. Additionally, patients with comorbidities such as chronic heart, lung, liver or renal disease, malignancy, immune suppression, or alcoholism are at higher risk of developing macrolide resistance [20]. Interestingly, macrolide use can also predispose to penicillin resistance in *S. pneumoniae* [21].

Common mechanisms of macrolide resistance include efflux pumps mediated by mefA/E (the so-called M phenotype) and ermA-M genes encoding for methylation of the 23s RNA thereby blocking macrolide binding. The ermA-M mutation also confers resistance to lincosamides (clindamycin) and streptogramin B antibiotics, earning the name 'MLS phenotype' [22, 23], and is associated with high-level macrolide resistance (minimum inhibitory concentration [MIC] >64 μg/mL) [16]. Fortunately, the predominant mechanism of resistance in *S. pneumoniae* in North America is the M phenotype, resulting in lower-level resistance; however, this may be changing [24].

Immune Modulation

Macrolide antibiotics have been shown to possess immune-modulating properties independent of their antimicrobial activity [25]. Their beneficial effect in chronic inflammatory lung diseases such as diffuse panbronchiolitis [26], cystic fibrosis [27], bronchiectasis [28], bronchiolitis obliterans syndrome [29], asthma [30], and COPD [31] are well documented. However, their benefit in the setting of acute pulmonary inflammation, as in CAP, is not as well established.

Proposed mechanisms of immune modulation are broad. They include suppression of pro-inflammatory cytokines [32], such as bacterial endotoxin-induced secretion of IL-8 [33] and IL-6 [34], decreased polymorphonuclear (PMN) cell recruitment [34], attenuation of reactive oxygen species production [35], and modulation of key transcription factors such as activator protein-1 (AP-1) and nuclear factor kappa B (NFkB) [36]. In addition, macrolides can promote apoptosis [37], decrease airway mucus production [38], and affect cell-signalling pathways [39].

The best clinical evidence to date on the non-antibiotic effects of macrolides in pneumonia was demonstrated in a randomized, placebo-controlled trial in patients with sepsis and ventilator-associated pneumonia (VAP) [40]. Patients were treated with clarithromycin for 3 days versus placebo in addition to standard antimicrobial therapy for VAP. The authors found that the addition of clarithromycin resulted in accelerated resolution of VAP and weaning from mechanical ventilation, and delayed death in those who died of sepsis.

In addition, the authors measured markers of inflammation (serum IL-10, TNF-alpha, as well as the expression of various cytokines in stimulation assays) and apoptosis at baseline and for 6 days following treatment [41]. They found that treatment with clarithromycin restored the balance between pro-inflammatory versus anti-inflammatory mediators, resulted in more efficient antigen presentation, and increased apoptosis. These effects were more pronounced in patients with septic shock and multi-organ dysfunction.

Further study on the role of macrolides as anti-inflammatory agents, particularly in CAP, is required.

However, given our knowledge to date, this research area seems promising to say the least.

Outpatient CAP

Outpatient populations are those least likely to benefit from the non-antimicrobial effects of macrolides, as mild disease generally produces less inflammation and immune dysfunction. The more important question in this group is whether or not macrolide monotherapy provides sufficient antimicrobial coverage for CAP. Macrolides are ideal for the treatment of atypical pathogens; however, increasing *S. pneumoniae* resistance [9, 15, 42] may result in treatment failures with macrolide monotherapy.

The largest study published to date examining the use of macrolides in the treatment of outpatients with CAP is a prospective cohort of almost 3000 patients [43]. The authors found that compared with respiratory fluoroquinolone monotherapy, macrolide monotherapy decreased 30-day mortality (adjusted odds ratio [aOR] 0.28; 95 % CI 0.09–0.86, $p=0.03$), as well as the composite outcome of 30-day mortality and hospitalization. Although the authors adjusted for pneumonia severity index (PSI), the macrolide group was significantly younger and had fewer comorbidities.

Skalsky et al. [44] performed a systematic review and meta-analysis of randomized controlled trials (RCTs) for CAP, comparing macrolides to respiratory fluoroquinolones. Both were most often used as monotherapy. In a subgroup analysis of mostly outpatients, there was no difference in mortality (relative risk [RR] 0.96; 95 % CI 0.53–1.72). Another systematic review and meta-analysis of RCTs in outpatients with CAP [45] was limited by trial number. However, macrolide therapy was not associated with increased clinical cure when compared to respiratory fluoroquinolones in any of the analyses.

Finally, a systematic review and meta-analysis of RCTs and quasi-RCTs evaluating the treatment of lower respiratory tract infections (LRTIs) with azithromycin versus amoxicillin or amoxicillin-clavulanic acid was recently published [46]. LRTI included acute bronchitis, acute exacerbation of COPD, and CAP. There was no difference in clinical failure rates between treatment groups in the combined LRTI population, although the acute bronchitis subgroup had fewer clinical failures with azithromycin (RR 0.63; 95 % CI 0.45–0.88). We postulate this might have been due (at least in part) to the anti-inflammatory properties of macrolides, as acute bronchitis is commonly non-bacterial in aetiology [47–49].

Based on this data, macrolide monotherapy in outpatient CAP is still an excellent option in patients without risk factors for pneumococcal resistance. Even with increasing resistance rates, however, there is evidence that low-grade efflux pump-mediated resistance might not be clinically relevant [50].

Inpatient, Non-severe CAP

The overall association between macrolide-containing regimens and improved outcomes in ward patients with CAP is based predominantly on observational data.

The Infectious Diseases Society of America (IDSA) guidelines for CAP [20] recommend a beta-lactam/macrolide combination or respiratory fluoroquinolone monotherapy in hospitalized patients with CAP not requiring intensive care. This is based on retrospective data [51–54] suggesting increased mortality with beta-lactam monotherapy. The European guidelines for lower respiratory tract infections [55] differ, however, as they do endorse beta-lactam monotherapy, despite the lack of atypical coverage.

The European statement is justified by evidence from two large meta-analyses [56, 57] of randomized data, including a Cochrane review. Both showed no mortality difference between beta-lactam monotherapy and antimicrobial regimens including atypical coverage. An updated review [58] continues to support this. However, macrolide monotherapy was included as a comparator to beta-lactam monotherapy in this analysis, which is problematic. This regimen is guideline discordant and therefore should not be used in comparison to beta-lactam monotherapy. Luckily, new studies are able to provide further insight.

Beta-lactam monotherapy and beta-lactam/macrolide therapies were recently compared in a large meta-analysis of observational studies by Nie et al. [59], demonstrating decreased mortality with beta-lactam/macrolide therapies compared to beta-lactam monotherapy (OR 0.67; 95 % CI 0.61–0.73, $p<0.001$, $I^2=3$ %). This meta-analysis included almost 43,000 inpatients from 16 studies and demonstrated only low to moderate heterogeneity. Results were robust to multiple sensitivity analyses.

Subsequently, Postma et al. [60] performed a cluster-randomized crossover trial to test the non-inferiority of a beta-lactam monotherapy strategy compared to beta-lactam/macrolide or respiratory fluoroquinolone therapies in inpatients with non-severe CAP. In their primary analysis of 90-day mortality, the beta-lactam monotherapy strategy was non-inferior to either alternate strategy. Though these results are certainly noteworthy, preadmission antibiotic exposure and/or deviation from the assigned strategy in up to one quarter of patients limits the validity of the results. As well, microbiological data was lacking.

Lastly, in another trial [61], the authors were unable to demonstrate non-inferiority of beta-lactam monotherapy compared with beta-lactam/macrolide therapy for clinical stability at 7 days. In this open-label, randomized controlled trial of 580 non-severe CAP inpatients, 7.6 % fewer patients in the beta-lactam monotherapy arm reached clinical stability at 7 days. There were no differences in 90-day mortality.

Though the weight of observational data still sits clearly in favour of beta-lactam/macrolide therapy over beta-lactam monotherapy for non-severe inpatient CAP [59], the new randomized data certainly challenges this conclusion, particularly with regard to mortality. We would comment that if clinicians increasingly decide to prescribe beta-lactam monotherapy in hospitalized patients with CAP, this may result in the secondary benefit of decreased population-level macrolide resistance.

Next, the discussion of inpatient CAP requires a comparison of the relative efficacies and safety of guideline-concordant therapies—beta-lactam/macrolide combination therapy versus respiratory fluoroquinolone monotherapy. These therapies are recommended in CAP guidelines based primarily on retrospective observational data. Without taking into account local susceptibilities, the two regimens are largely equivalent in antimicrobial spectra.

A large prospective study by Asadi et al. [62] examined mortality in non-ICU inpatients with CAP. In an adjusted analysis, there was no difference in mortality between beta-lactam/macrolide and respiratory fluoroquinolone groups; however, the beta-lactam/macrolide strategy had a greater risk of ICU admission as well as the composite outcome of ICU admission and death, suggesting they might have been sicker comparatively.

A subsequent systematic review and meta-analysis of observational studies and RCTs comparing macrolide versus non-macrolide-containing regimens [63] demonstrated decreased mortality with the use of macrolides (RR 0.78; 95 % CI 0.64–0.95, p=0.01, I^2=85 %). However, this effect was lost when the analysis was limited to RCTs and when observational trials of large administrative databases were excluded. Perhaps more importantly, a pre-defined subgroup analysis of guideline-concordant beta-lactam/macrolide versus respiratory fluoroquinolone therapies revealed no difference in mortality (5.3 % for beta-lactam/macrolide versus 5.8 % for respiratory fluoroquinolones, p=0.22).

Finally, a systematic review and meta-analysis by Skalsky et al. [44], including only RCTs, examined both inpatients and outpatients with CAP. Macrolides, either alone or in combination, were compared with respiratory fluoroquinolones. There was no mortality difference between the groups, including when inpatient and outpatient groups were analysed separately.

In summary, these data suggest macrolides—when used in combination—*may* be associated with decreased mortality in ward patients with CAP. Of course, most of the studies suggesting a benefit are retrospective and inherently subject to confounding. Although randomized trial data is limited, the available evidence suggests that for non-severe inpatient CAP, beta-lactam/macrolide versus respiratory fluoroquinolone regimens are equivalent. This supports 2007 IDSA guidelines. Additionally, this data suggests that adherence to guidelines may be more important than the specific antimicrobial choice. Therefore, we would suggest that therapy in inpatient CAP not only be guideline concordant but also guided by recent antibiotic use and individual patient characteristics [20].

Inpatient, Severe CAP

The study of severe CAP is inherently difficult. Most data are observational and the complexity of this heterogeneous group makes statistical adjustment challenging. When attempted, adjustments often do not include markers of illness severity such as the Acute Physiology and Chronic Health Evaluation (APACHE) II score, or important confounders such as glucocorticoid use. In addition, varied definitions of severe CAP (by PSI, IDSA criteria, or ICU admission) and a wide range of subpopulations in this group (such as those requiring mechanical ventilation or presenting in septic shock) make combining and comparing studies difficult.

Other limitations when studying severe CAP include highly variable antimicrobial regimens and the use of historical cohorts that may not reflect contemporary outcomes. Lastly, data on microbial aetiology is often not available, making it difficult to know if empiric therapies were effective. Clearly inappropriate empiric antimicrobial therapy has been associated with poor outcomes in a number of studies [64–66].

A systematic review and meta-analysis of patients admitted to the intensive care with CAP provides the most comprehensive data on macrolide therapy and mortality [67]. This review included 28 observational studies and almost 10,000 critically ill patients with CAP. In an adjusted analysis of macrolide versus non-macrolide-containing regimens, a significant mortality benefit was observed (RR 0.75; 95 % CI 0.58–0.96, p=0.02, I^2=57 %). The major limitation of this meta-analysis was the sole inclusion of observational data.

A recent, large prospective cohort [68] study examining the association between adequate initial antibiotic coverage and survival in severe CAP patients demonstrated no difference in mortality between beta-lactam/macrolide and beta-lactam/respiratory fluoroquinolone groups at 60 days. Adjustment for multiple factors including Simplified Acute Physiology Score (SAPS) II, receipt of mechanical ventilation, presence of septic shock, and use of glucocorticoids was rigorously performed.

In a prospective cohort study [69] including only intubated CAP patients, a mortality benefit was observed with beta-lactam/macrolide therapy compared with beta-lactam/respiratory fluoroquinolone therapy (aHR 0.48; 95 % CI 0.23–0.97, p=0.04). Notably, patients in both groups received guideline-concordant therapies. Groups were equivalent in terms of age, major comorbidities, incidence of bacteremia, and illness severity scoring.

However, the beta-lactam/respiratory fluoroquinolone group received piperacillin-tazobactam or a carbapenum more often than the beta-lactam/macrolide group (48 vs. 6.5 %). The choice of broader-spectrum therapy may reflect unfavourable clinical features in the beta-lactam/respiratory fluoroquinolone group despite seeming similar by recorded characteristics.

For those with CAP and severe sepsis, retrospective observational data [70] also suggests decreased 30-day mortality with macrolide-containing regimens compared with non-macrolide therapies (aHR 0.3; 95 % CI 0.2–0.7). However, several important comorbidities were significantly less frequent in the macrolide group and not adjusted for in the analysis beyond inclusion in the PSI score.

Lastly, macrolides have also been associated with decreased in-hospital and 30-day mortality in a retrospective study of bacteremic CAP [71]. As well, in patients with pneumococcal bacteremic CAP, a mortality benefit was observed with the addition of a macrolide [72]. Despite adequate treatment with a beta-lactam, patients who did not receive macrolides experienced higher adjusted mortality. This potentially suggests a non-antimicrobial, immune-modulatory mechanism of effect as discussed previously.

Although randomized trial data in severe CAP is limited, a meta-analysis of RCTs by Vardakas et al. [73] compared respiratory fluoroquinolone therapy to beta-lactam/macrolide combination, or beta-lactam or macrolide monotherapies. In the severe CAP subgroup, treatment success was highest in the respiratory fluoroquinolone group versus all other comparator regimens, although at least some of the comparators were guideline discordant [74–76]. In addition, most trials were unblinded and some lacked intention-to-treat analyses.

In summary, there is a paucity of randomized trial data examining the association between macrolide therapies and mortality in patients with severe CAP. Most of the available data is observational in nature and therefore subject to confounding; however, it does suggest a mortality benefit with macrolide use. The mechanism by which a mortality benefit may be conferred is also unclear. The antimicrobial effect of macrolides on atypical pathogens is one possibility. Second, macrolides may attenuate the inflammatory response in critically ill patients who are at higher risk of systemic inflammatory response syndrome (SIRS) compared to non-ICU cohorts. In fact, studies demonstrate increased markers of inflammation in this population [77], and animal models of pneumonia have demonstrated a reduction in inflammatory markers as well as improved histopathology of lung tissue with macrolide therapy [78].

Unfortunately, the design of a randomized trial that is needed to compare optimal antibiotic regimens in severe CAP—specifically macrolide vs. non-macrolide-based therapies—offers a unique set of challenges. Most important would be a treatment arm with a regimen that is concordant with the IDSA guidelines and a very large number of patients required to detect a mortality benefit if one truly exists, necessitating multicenter, and likely multinational, collaboration to complete such an effort. Until such a study is completed, we support current IDSA guidelines in the treatment of severe CAP.

Adverse Effects

The most serious adverse event associated with macrolide therapy is cardiotoxicity, specifically fatal arrhythmias. However, several reviews suggest that the absolute risk of this event is actually very low [79, 80]. Azithromycin is felt to have the least cardiotoxicity [81] within the macrolide class and is generally preferred. A recent systematic review examining the association between azithromycin and cardiovascular death [82] found only six case reports of QT prolongation and three cases of fatal arrhythmia reported in the literature between 1946 and 2013. Notably, all patients had underlying cardiac disease and other potentially confounding risk factors or medications.

Another recent retrospective cohort study [83] demonstrated increased risk of cardiovascular death with azithromycin compared to no antibiotic therapy, however, demonstrated no difference when compared with penicillin. A second, large retrospective cohort of outpatients [84] found a small absolute increase in cardiovascular deaths in patients treated with azithromycin compared with amoxicillin and ciprofloxacin but not when compared to levofloxacin. The risk of cardiovascular death was most pronounced among patients with a high baseline risk of cardiovascular disease. The retrospective nature of these studies, as well as derivation from large administrative databases lacking clinical information, limits reliability of their results. Most importantly, the underlying indication for antibiotic use in these studies was not controlled for.

In an attempt to further clarify this issue, Mortensen et al. [85] examined cardiovascular events and all-cause mortality in elderly patients admitted with CAP. Although they found a higher risk of myocardial infarction in those treated with azithromycin, there was no increase in risk of any cardiac event or arrhythmia. Most importantly, the overall 90-day mortality was actually lower in the azithromycin group (OR 0.73; 95 % CI 0.70–0.76, $p<0.001$), demonstrating a net benefit associated with azithromycin therapy.

In summary, the absolute risk of macrolide-induced cardiotoxicity is low [79, 80, 82]. When choosing therapy for an individual patient, side effect profiles must be considered for all potential antimicrobial agents. Concurrent use of other QT-prolonging drugs may be a significant contributor to the true risk. In accordance with common clinical practice, the

risks and benefits of macrolide therapy, and a review of other concurrent medications, must be performed prior to prescription in each patient.

Discussion

This review summarizes contemporary data on the use of macrolides in CAP. Macrolides are commonly used in the treatment of CAP based on various guideline recommendations. Macrolides have also been shown to improve outcomes in a number of chronic lung conditions due to their immunomodulatory effects. The mechanisms of action in acute CAP are less clear, but we postulate may be both antimicrobial and anti-inflammatory in nature.

Macrolide monotherapy for outpatient CAP is still an appropriate strategy and remains supported by guidelines. Theoretically, azithromycin offers the broadest coverage and has the most favourable side effect profile. Resistance in both *S. pneumoniae* and Mycoplasma is increasing globally, however, limiting the use of macrolides in patients with recent macrolide exposure [2, 4, 22, 23].

Outcome data in inpatients with non-severe CAP generally support current IDSA guidelines. A mortality benefit with macrolide-based regimens may exist, based on one large meta-analysis of observational studies [63]; however, higher quality data is needed. New data examining beta-lactam monotherapy in inpatient CAP is particularly interesting [60, 61] and also warrants further study.

Observational data also suggests macrolides may be associated with decreased mortality in severe CAP [67], including those with severe sepsis [70]. This benefit may be due to immune modulation given systemic inflammation is common in this patient population. Unfortunately, there is a paucity of randomized trial data comparing macrolide versus non-macrolide therapies and guideline-concordant regimens—in general—in severe CAP. Contradictory observational data confuses the issue further. Until further randomized trial data is available, current guideline-concordant regimens should be considered equivalent.

Finally, the need for a well-designed, randomized trial to assess CAP outcomes with current guideline-concordant regimens is essential. Without this, we have effectively reached the limit of our knowledge. Critically ill patients may have the greatest potential gain with further study, though these patients are also the most logistically challenging to study. Many outcomes other than mortality should also be examined—such as treatment failure, need for hospitalization as well as readmissions, hospital (and ICU) lengths of stay, and adverse events. In fact, these outcomes may be more appropriate (versus mortality) to study in patients with mild to moderate CAP. Meanwhile, ongoing etiologic research and surveillance of antimicrobial resistance are essential in evolving CAP treatment strategies over time.

Conclusions

In conclusion, macrolides are safe and effective therapies in CAP. Risk factors for macrolide resistance must be considered to avoid inappropriate prescriptions. The potential immune-modulatory properties of macrolides may be particularly beneficial in patients with systemic inflammatory response syndrome—specifically those with severe CAP—however further study is required. Despite the fact that observational data suggests a mortality benefit with macrolide therapies, higher quality randomized trial data is needed. Sufficient equipoise exists to warrant this large undertaking. Until then, IDSA CAP guidelines should guide empiric therapy.

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Compliance with Ethical Standard

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