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REVIEW ARTICLE

A Review of Macrolide Based Regimens for Community-Acquired Pneumonia

Forest W. Arnold [†], *Leslie A Beavin*

Abstract

Community-acquired pneumonia (CAP) has significant morbidity and mortality. The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines recommend two antimicrobial regimens for hospitalized patients with CAP, one of which includes a macrolide, and one of which does not. Both regimens have antimicrobial properties, but macrolides also possess immunomodulatory properties. Macrolides, however, may also have potential arrhythmia adverse effects. The purpose of this review is to provide an update of studies evaluating outcomes for patients with CAP treated with or without a macrolide-based regimen. Two recent randomized controlled trials conflict with each other regarding the benefit versus noninferiority of including a macrolide for the treatment for CAP. Each have their respective limitations. Most prior observational studies and meta-analyses favor using a regimen with a macrolide. We do not recommend any different treatment strategy than the current IDSA/ATS guidelines for CAP. Further studies need to occur to define the optimal treatment for CAP.

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Affiliations:
University of Louisville Division of Infectious Diseases, Louisville: (FWA, LAB)

1 Background

Community-acquired pneumonia (CAP) is the 8th leading cause of death in the US.[1] In this country, CAP is the most common cause of admission to the ICU and causes the highest mortality of any infectious disease. Inpatient mortality in a recent study of all hospitalized patients in Louisville, KY (population ~600,000) was 6%.[2] The Non-ICU mortality rate may be as low as 2%, while the ICU mortality rate may be as high as 18%, or higher.[3,4] Length of stay accounts for the bulk of expenditure on CAP. It requires a major contribution of resources for health care in the US. Estimates are ~$1000 per day for care on wards, $3800 to $5000 per day in the ICU.[4] A total of $16 billion was spent for CAP in 2013.[5]

Streptococcus pneumoniae has been the primary pathogen isolated for over a century in patients with CAP. The onset of resistance to *S. pneumoniae* presented with the introduction of penicillin, and has broadened to other β-lactams, macrolides, and fluoroquinolones as they have been introduced. A surveillance study of 71 centers in the US yielded 3329 consecutive samples.[6] Resistance to ceftriaxone was 2%, to erythromycin was 39%, and to levofloxacin was 0.7%. Resistance of *Haemophilus influenzae* and *Moraxella catarrhalis* to the same three drugs was between zero and 1.3%. Atypical pathogens (*Legionella pneumophila*, *Chlamydia pneumoniae*, and *Mycoplasma pneumoniae*) have a worldwide incidence up to 22%.[7] β-lactams do not cover *L. pneumophila* or *C. pneumoniae* because they are intracellular organisms, nor do they cover *M. pneumoniae* because it lacks a cell wall, but the pathogens are covered by macrolides and fluoroquinolones. *Staphylococcus aureus* causes CAP more so now than in decades past. Risk factors for CAP due to *S. aureus* include colonization with *S. aureus* in the nares, performance in contact sports, injection drug use, men who have sex with men, and living in crowded living conditions (including prison). Pseudomonas is rare in CAP, but may occur in those with bronchiectasis or chronic obstructive pulmonary disease, especially after long-term antimicrobial or glucocorticoid use. Treatment should be focused on the most common pathogens in consideration with unique risk factors of each patient.

The primary recommendation for the treatment for CAP by the American Thoracic Society/Infectious Diseases Society of America is to provide ward patients with either a β-lactam plus a macrolide or a fluoroquinolone.[8] There has not been enough convincing evidence for either regimen to favor one over the other. In the ICU, a β-lactam is recommended to be combined with either a macrolide or a fluoroquinolone. Other coverage is based on risk factors for specific pathogens, such as methicillin-resistant

[†]Correspondence To: Forest W. Arnold, DO, MSc
501 East Broadway; Suite 140B; Louisville, KY 40202
Email: f.arnold@louisville.edu

S. aureus or Pseudomonas. Physicians should still exercise clinical judgment as it is considered to be integral to the management of CAP.[9] Guideline-concordant therapy was shown to be associated with improved outcomes in ICU patients and the elderly, but not in ward patients.[10–12]

2 Macrolide antimicrobials

2.1 History of pathogen coverage

Macrolides were first discovered from the soil bacterium *Streptomyces erythraeus* in the 1950s. Erythromycin contains a large 15 member ring. Azithromycin followed and is distinct from erythromycin by having a single nitrogen substituted for a methyl group. With this small change, azithromycin has better oral absorption with less gastrointestinal side effects, and a longer half life. Although it is slightly less active than erythromycin for Streptococcus pneumoniae, it has better coverage for *H. influenzae*, *M. cararrhalis* and *L. pneumophila*.

2.2 Resistance

Resistance to macrolides is conferred by either efflux of the drug from the cell or a target site alteration. The most notable efflux mechanism, called the M phenotype, is expressed by *S. pneumoniae*. The gene *mef*(A) codes for an efflux pump that stretches across the entire cytoplasmic membrane of *S. pneumoniae* and pumps the macrolide out of the pathogen. The M phenotype is the most predominant one in the US for S. pneumoniae.[13] The most predominant resistance phenotype in Europe is a target site alteration referred to as MLS_B phenotype.[14] When methylation of a specific adenine in the gene that codes for the 23S ribosomal RNA of the 50S ribosomal subunit occurs, it then confers resistance to macrolides by several pathogens, including S. pneumoniae. This pattern of resistance, noted as MLS_B phenotype, is coded by the *erm* (erythromycin ribosome methylation) gene. The enzyme that carries out methylation can be induced by low levels of erythromycin. The "D" test was made popular when it was used to verify the presence or absence of clindamycin resistance to *S. aureus*. Samples that may have been initially found to be "sensitive", were concluded to be "resistant" after inducible resistance was detected in the presence of erythromycin.

2.3 Anti-inflammatory activity

Macrolides, in addition to having antimicrobial effects, have the unique characteristic of anti-inflammatory effects. These include inhibition of proinflammatory cytokines and proteins, such as nuclear factor κB, activating protein-1, interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor-α.[15,16] Macrolides stimulate endothelial cells to release nitric oxide while they alter epithelial cells to resist pneumococci.[17,18] Biofilm formation by bacteria is interrupted while mucociliary clearance is increased.[19] There is interference with the production of reactive oxygen species (ROS) by neutrophils.[19] Finally, neutrophil apoptosis is accelerated, favoring it over necrosis resulting in more programmed cell death rather than caustic cell contents being released during necrosis.[20]

2.4 Adverse effects

Macrolides are more known for their side effects, such as nausea, than adverse effects. When azithromycin was created substituting a nitrogen for a methyl group, absorption improved, thus curbing the gastrointestinal effects. The alteration of the molecule, however, did not alter the potential for arrhythmia. The most well known adverse effect is QTc prolongation with potential Torsades de Pointes leading to ventricular fibrillation and death. A study of a Tennessee Medicaid database sought to determine if azithromycin, amoxicillin or a fluoroquinolone was associated with cardiac-related death as compared to a control group (no antimicrobial).[21] Azithromycin was found to be associated with cardiovascular death more so than amoxicillin (Hazard ratio (HR); 95% confidence interval (CI) 1.38-4.50; P=0.002), or no antimicrobial (HR 2.88; 95% CI 1.79-4.63; P<0.001). There was no significant difference between azithromycin and levofloxacin (P=0.18), but there was between azithromycin and ciprofloxacin (HR 3.49; 95% CI, 1.32-9.26; P=0.01). For this reason, potential cardiac-related death should be considered when prescribing anyone azithromycin or levofloxacin. It should be noted, however, that there were over 3.5 million patients included in this study, which makes a difference between groups more likely to be statistically significant. The proportions of patients affected were very small (0.003% for amoxicillin and 0.008% for azithromycin). At this time, neither azithromycin nor levofloxacin have a black box warning related to arrhythmia.

Other large cohort studies found no effect or a protective effect of azithromycin on cardiovascular outcomes. The first study was a similar age population among VA patients as the previous study with Medicare patients.[30] All patients had been hospitalized for pneumonia, and the mean age was 77 years. There were almost 40,000 in each group studied: those who received azithromycin and those who did not. The 30 d-day and 90-day mortality were both statistically significantly lower in the azithromycin group. The 90-day mortality in each group was 17.4% vs 22.3%; odds ratio 0.73 (95% CI 0.70-0.76). Among four separate outcomes–any cardiovascular event, heart failure and cardiac arrhythmia–were similar, while myocardial infarction occurred more in the azithromycin group; OR 1.11 (95% CI, 1.03-1.20). The other study included patients between ages 10-64 years who did not necessarily have CAP, and were prescribed either azithromycin (1.1 million episodes), penicillin V (7.4 million episodes) or no antibiotic (1.1 million episodes).[31] Mortality from cardiovascular causes for azithromycin was 1.1/1000 patient-years, which was compared to no antibiotic, 0.4/1000 patient-years (rate ratio 2.85; 95% CI, 1.13-7.24), and penicillin V, 1.5/1000 patient-years (rate ratio 0.93; 95% CI, 0.56-1.55).

3 Literature Review

Attention has been given to compare a β-lactam plus a macrolide versus a fluoroquinolone alone, which are the two regimens recommended in the guidelines.[8] In general, studies that have shown a benefit of a macrolide containing regimen have been observational studies with a "real-world" population of mixed severities as measured by the pneumonia severity index or a version of the CURB-65 (Confusion, blood Urea nitrogen level, Respiratory rate, Blood pressure–age $\geq$65 years). Prospective, randomized clinical trials (RCT) have opposite conclusions. **Table 1** summa-

Table 1 Efficacy of antimicrobial regimens with and without a macrolide for hospitalized patients with community-acquired pneumonia.

Study	Year	Method	Population	Regimens	Outcomes	Results comparing macrolide and non-macrolide therapy
Gleason et al [22]	1999	Observational	12,945 Medicare patients ≥65 yrs	Ceph alone, Ceph + Mac, Quin alone	30-d mortality	Cephalosporin alone worse than other two regimens
Loh et al [23]	2005	Prospective, observational	141 non-severe and severe patients	Mac *vs* Non-mac	In-hospital mortality	No difference between groups
Aspa et al [24]	2006	Observational	638 patients with pneumcoccal CAP	β-lac alone β-lac + Mac Quin alone	30-d mortality	No difference between groups
Dwyer et al [25]	2006	Prospective, observational	370 patients with pneumococcal bacteremia	β-lac *vs* β-lac + Mac	Mortality (not specified)	No difference between groups
Lodise et al [26]	2007	Observational	515 VA patients	β-lac + Mac *vs* Quin alone	14-d and 30-d mortality	Combination group had better 14-d mortality (full population), and 30-d mortality (severe CAP only)
Metersky et al [27]	2007	Observational	2,209 Medicare patients	Non-mac *vs* Mac	In-hospital mortality, 30-d mortality, 30-d readmit rate	All outcomes favored Mac group
Paul et al [28]	2007	Prospective, observational	451 patients; only 54 after propensity analysis	β-lac *vs* β-lac + Mac	30-d mortality	β-lac + Mac group with favorable difference, but not after statistical adjustment
Restrepo et al [29]	2009	Observational	237 patients with severe sepsis	Mac *vs* Non-mac	30-d and 90-d mortality	Both outcomes favored Mac group

rizes pertinent studies.

The first of two RCTs was an open-label, multicenter Swiss study in 2014 of 580 hospitalized patients, which divided patients between two arms: β-lactam alone versus β-lactam plus a macrolide.[32] The patients were immunocompetent and excluded anyone presenting with a pneumonia severity index risk class of V, therefore the primary outcomes were the proportion who reached clinical stability within a week (59% for the monotherapy arm vs 66% for the combination therapy arm; P=0.07), and the 30-day readmission rate (7.9% for the monotherapy arm vs 3.1% for the combination therapy arm; P=0.01). Other outcomes did not differ including mortality, length of stay, transfer to ICU and recurrence of pneumonia within 90 days.

The second RCT was a cluster-randomized, crossover study in the Netherlands in 2015 of 2,283 patients divided among three arms: β-lactam alone, β-lactam with a macrolide, and fluoroquinolone alone.[33] The mortality in each group was 9.0%, 11.1% and 8.8%, respectively. Analyses were compared relative to the β-lactam alone group, which showed noninferior results with confidence intervals crossing 1. The major limitation of the study was the fact that 39% of the patients in the β-lactam monotherapy group received an antimicrobial covering an atypical pathogen at some point during the hospitalization.

A prospective, observational English study evaluated 5,240 patients who received either a β-lactam alone or a β-lactam plus a macrolide.[22] Mortality was 26.8% in the monotherapy group and 23.0% in the combination therapy group; P=0.001. ICU admission, need for mechanical ventilation, and need for inotropic support were not statistically different.

One early retrospective study evaluated length of stay and mortality based on the use of a macrolide in particular. With <100 patients enrolled, however, statistical significance was not expected, nor attained.[23] Another larger study in 1999 of Medicare patients aged ≥65 years recorded 30-day mortality for patients receiving various antimicrobial regimens.[24] Those treated with a fluoroquinolone or cephalosporin plus a macrolide had lower 30-day mortality compared to those who received a cephalosporin alone.

During this same time period, there were studies that did not find a difference with the addition of a macrolide to CAP treatment. A small single center study in an urban teaching hospital in Malaysia evaluated patients with and without macrolide therapy for CAP.[25] Among 141 patients, mortality was 9% in each group. They did perform a subgroup analysis on the severe patients, but there were too few for any statistical difference. A multi-institutional study in Spain of 638 patients with CAP due to S. pneumoniae compared mortality between different antimicrobial groups with the reference group having received a β-lactam plus a macrolide.[28] Neither the β-lactam group nor the fluoroquinolone group was statistically different. A separate international study in four centers with 340 patients with CAP complicated by pneumococcal bacteremia compared outcomes between patients who received a β-lactam alone (n=261) to those who received a β-lactam plus a macrolide (n=79).[27] Predictors of death after multivariate analysis were age, pneumonia in ≥2 lung lobes and higher severity of disease, but not antimicrobial regimen. The mortality for the β-lactam group was 11% vs 19% for the β-lactam plus a macrolide group (P=0.08). A study from three centers in Germany, Israel, and Italy compared mortality in CAP patients who received either a β-lactam (n=169) or a β-lactam plus a macrolide (n=282).[26] The mortality was 22% vs 7% (P=0.0001), respectively, but when the authors adjusted for confounding factors using propensity score matching to account for differences in each group, they were only able to compare 27 patients in each group, erasing any statistical difference. The differences they accounted for, and for which they excluded patients from analysis, were septic shock, mental status changes, and having an infiltrate on chest radiograph.

In the last ten years, studies have been designed to determine if combination therapy or fluoroquinolone therapy is associated

with better outcomes. Among 2209 CAP Medicare patients in the US treated with a macrolide or with a fluoroquinolone, multivariable analysis showed that regimens containing a macrolide had lower in-hospital mortality (P=0.01), lower 30-day mortality (P=0.007), and lower 30-day readmission rates (P=0.004).[29] In a study from a VA hospital in New York, 515 patients either received combination or fluoroquinolone therapy for CAP.[34] Improved mortality was found in patients with severe (PSI risk class V) CAP. For these severe patients, 14-day mortality for the β-lactam plus a macrolide group was 8.2% versus 28% for the fluoroquinolone group (P=0.02); and 30-day mortality was 18.4% vs 36.6% (P=0.05), respectively.

A subsequent study in Texas evaluated mortality in patients with severe CAP.[35] Patients were identified by ICD-9 coding, had positive imaging for pneumonia, and fulfilled the traditional criteria for severe sepsis with at least one organ dysfunction as defined by Bone et al.[36] IDSA/ATS guideline-concordant therapy was determined in a macrolide group (97%) and a non-macrolide group (63%). Longer-term outcomes were assessed as 30- and 90-day mortality in each group. Among 237 patients, 44% received a macrolide. The 30-day mortality for the β-lactam plus a macrolide group versus the non-macrolide group was 11% vs 29% (P=0.001), while the 90-day mortality was 12% vs 34%, respectively. Interestingly, among patients with macrolide-resistant pathogens, the macrolide group had a lower risk of dying within 24 days than the non-macrolide group by multivariable analysis (HR 0.10, 95% CI 0.02-0.49; P=0.005). A follow-up study included ICU patients, all of whom received guideline-concordant therapy, who were in a β-lactam plus a macrolide group or a β-lactam plus a fluoroquinolone group.[37] The 30-day mortality for the macrolide containing regimen group was 26% vs. 46% for the fluoroquinolone containing regimen group (P=0.04). This statistical difference was maintained after adjusting for etiology and severity (HR 0.48%, 95% CI 0.23-0.97, P=0.04).

Outside of the US, including some countries in Europe, guidelines recommend using a β-lactam alone in some in-patients with CAP. A study from Germany evaluated ~1800 hospitalized patients with CAP who were either treated with a β-lactam alone or a β-lactam plus a macrolide, but there were only enough patients with lower risk (CRB65 score 0, 1 or 2) to statistically analyze.[38] Among 827 patients who received a β-lactam plus a macrolide and 919 who received a β-lactam alone, the 14-day mortality was only different for those with a CRB-65 score of 2 (2.9% vs 11.4%, respectively). There was no difference for those with a lower CRB-65 score or for any severity group when evaluating 30-day mortality.

At least two meta-analyses have been performed comparing antimicrobial treatment for CAP. The first was in 2012 and reviewed 12 out-patient, and four in-patient studies from 1993 to 2005.[39] Most patients had mild to moderate CAP. Each study that was reviewed compared regimens that included a fluoroquinolone to regimens that included a macrolide. For 30-day mortality, there was no difference. Clinical failure was defined as persistence of signs and symptoms to the extent that treatment was changed, or there was a lack of radiographic improvement within four weeks. Clinical failure was more frequent with a macrolide containing regimen than a fluoroquinolone containing regimen (relative risk (RR) 0.78, 95% CI, 0.67-0.91). Microbiological failure was presumed to be growth of the organism from a specimen collected after treatment completed. This outcome was also lower with fluoroquinolones (RR 0.63, 95% CI, 0.49-0.81). Although fluoroquinolones had less clinical and microbiological failure, the clinical significance of the advantage was deemed to be unclear. Fluoroquinolones were also favored regarding the frequency of adverse events, which led to the practical benefit of more completions of a full course of the antibiotic.

The other meta-analysis was in 2016, and reviewed 14 studies from 1999 to 2015 including hospitalized patients exclusively.[40] Each study that was reviewed compared either a β-lactam plus a macrolide or a fluoroquinolone alone to a β-lactam alone. Among data provided, 17 antimicrobial comparisons were available to analyze from the 14 studies. All of the studies except one had an odds ratio that favored initially prescribing a β-lactam plus a macrolide or a fluoroquinolone over a β-lactam alone. Ten of the studies had a 95% CI that did not cross 1 supporting a β-lactam plus a macrolide or a fluoroquinolone alone over a β-lactam alone. These results support the IDSA/ATS guidelines for CAP. The two meta-analyses support the general finding that a statistical difference is stronger as the population studied has more severe disease.

4 Conclusions

After years of observational studies evaluating the use of a regimen containing a macrolide, two RCTs were performed, but with antagonistic conclusions–one that found that a β-lactam alone for patients with CAP was noninferior to a β-lactam plus a macrolide, and one that did not. Because of the varying data, some CAP guidelines from outside of the US allow for β-lactam monotherapy in certain patients. But, in light of the different populations studied in the RCTs (one exclusively in-patients, one a mix of in- and out-patients), the limitations of the RCTs, and the great majority of observational studies that favor the use of a macrolide containing regimen for CAP, the recommended therapy by IDSA/ATS at this time is either a β-lactam plus a macrolide or a fluoroquinolone alone for hospitalized patients with CAP.

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