Macrolide-Based Regimens and Mortality in Hospitalized Patients With Community-Acquired Pneumonia: A Systematic Review and Meta-analysis

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Background. Macrolides are used to treat pneumonia despite increasing antimicrobial resistance. However, the immunomodulatory properties of macrolides may have a favorable effect on pneumonia outcomes. Therefore, we systematically reviewed all studies of macrolide use and mortality among patients hospitalized with community-acquired pneumonia (CAP).

Methods. All randomized control trials (RCTs) and observational studies comparing macrolides to other treatment regimens in adults hospitalized with CAP were identified through electronic databases and gray literature searches. Primary analysis examined any macrolide use and mortality; secondary analysis compared Infectious Diseases Society of America/American Thoracic Society guideline-concordant macrolide/beta-lactam combinations vs respiratory fluoroquinolones. Random effects models were used to generate pooled risk ratios (RRs) and evaluate heterogeneity ($I^2$).

Results. We included 23 studies and 137,574 patients. Overall, macrolide use was associated with a statistically significant mortality reduction compared with nonmacrolide use (3.7% [1738 of 47,071] vs 6.5% [5861 of 90,503]; RR, 0.78; 95% confidence interval [CI], .64–.95; P = .01; $I^2 = 85$%). There was no survival advantage and heterogeneity was reduced when analyses were restricted to RCTs (4.6% [22 of 479] vs 4.1% [25 of 613]; RR, 1.13; 95% CI, 0.58–2.20; $P = .66$; $I^2 = 0$%) or to patients treated with guideline-concordant antibiotics (macrolide/beta-lactam, 5.3% [297 of 5574] vs respiratory fluoroquinolones, 5.8% [408 of 7050]; RR, 1.17; 95% CI, .91–1.50; $P = .22$; $I^2 = 43$%).

Conclusions. In hospitalized patients with CAP, macrolide-based regimens were associated with a significant 22% reduction in mortality compared with nonmacrolides; however, this benefit did not extend to patients studied in RCTs or patients that received guideline-concordant antibiotics. Our findings suggest guideline concordance is more important than choice of antibiotic when treating CAP.
regimens, but the findings have been mixed and are largely from observational studies [4–6].

The benefit of macrolides (eg, clarithromycin or azithromycin) has been postulated to be due to their immunomodulatory and anti-inflammatory properties [7, 8]. Their benefit as adjunct agents in chronic inflammatory pulmonary diseases such as diffuse panbronchiolitis [9], bronchiolitis obliterans syndrome [10], and even chronic obstructive pulmonary disorder [11] has been documented. Whether such macrolide-related benefits can be extended to acute inflammation, particularly pneumonia, remains unclear [4–6]. That said, despite increasing macrolide-resistance in Streptococcus pneumoniae, the reason for choosing these drugs for treatment of pneumonia is their antimicrobial effect, which often include coverage for atypical agents such as Mycoplasma, Legionella, Chlamydia phila in the spectrum of antimicrobial activity.

To our knowledge, no systematic review specifically examining the clinical impact of macrolide-based regimens in CAP patients has been reported. Therefore, we conducted a systematic review and meta-analysis to explore whether the use of macrolide-based regimens decreases mortality in patients hospitalized with CAP.

METHODS

Although it was not registered, the protocol for this study was developed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [12].

Search Strategy

An experienced librarian (L. T.) helped us conduct a comprehensive search of the following key electronic biomedical databases from inception through December 2011: Medline, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessments, Cochrane Central Register of Controlled Trials, Science Citation Index Expanded, Conference Proceedings Citation Index—Science, BIOSIS Previews, and Scopus. A modification of the Cochrane highly sensitive search strategy for identifying randomized trials [13] and study design filters from BMJ Clinical Evidence were applied in Medline and Embase. All available years from 1996 onward were searched without language restrictions. The search strategy is provided in the Supplementary Data.

In addition to electronic databases, we explored sources of gray literature, including the latest 4 years (2008–2011) of proceedings from the Infectious Diseases Society of America (IDSA), American Thoracic Society (ATS), Interscience Conference on Antimicrobial Agents and Chemotherapy Congress of Microbiology and Infectious Disease, the European Congress of Microbiology and Infectious Diseases, and the clinical trials registry ClinicalTrials.gov. Finally, we consulted with content experts and contacted authors of studies that might have data appropriate for our analysis. For the latter, we attempted up to 3 contacts with the corresponding (first and senior) author before considering them nonresponsive.

Study Selection

A checklist was used to assess whether studies met our inclusion criteria for population (hospitalized patients with CAP), exposure (macrolide antibiotic), comparison group (nonmacrolide antibiotic), outcome (mortality, even if it was not a primary or secondary outcome of the included study), and study design (randomized control trials [RCTs] and observational cohort studies). Exclusion criteria eliminated non-English or duplicate reports and studies on outpatients, critically ill patients, immunocompromised patients, or patients identified as having some form of healthcare-associated pneumonia (HCAP).

Data Collection

Two trained reviewers independently conducted study selection, abstracted data, and assessed the risk of bias (L. A. and W. I. S.). Discrepancies between reviewers were resolved through discussion and consensus; if consensus could not be reached, discrepancies were resolved by S. R. M. Risk of bias was evaluated as low, unclear, or high using the Cochrane risk of bias tool for RCTs [14]. For cohort studies, risk of bias was assessed using a modified version of the Newcastle–Ottawa scale that accorded a maximum of 8 points to each study, with ≤5 points indicating a high risk of bias [15].

Sources of Heterogeneity

Potential sources of heterogeneity were considered a priori. These included study design (RCTs vs observational studies) and source of patient population (large administrative database studies vs clinically rich databases). We therefore examined 3 prespecified subgroups: RCTs, observational cohort studies, and studies remaining after exclusion of large administrative database studies that were based on claims data or International Classification of Diseases (ICD) coding. Publication bias was assessed with Egger’s test [16], with the results considered to indicate bias when P < .05. In addition, we visually inspected funnel plots for asymmetry.

Synthesis of Data

We tabulated pertinent descriptive data from included studies. Using a random effects model, we meta-analyzed risk estimates using Mantel–Haenszel calculations to estimate pooled risk ratios (RRs). Heterogeneity was assessed using the I^2 test statistic and classified as low (≤25%), moderate (>25%–50%), and high (>50%). We did not prespecify any I^2 that would preclude meta-analytic pooling. We were unable to construct a meta-regression model given that data on potential
confounders (such as age, sex, disease severity) were not consistently available across all studies.

**Outcomes**

In our primary analysis, we examined the association between macrolide-based regimens (including macrolide monotherapy) and in-hospital or 30-day mortality. Recognizing that macrolide monotherapy does not provide adequate empiric therapy for all CAP pathogens (and is considered guideline “discordant” for this reason), potentially negating or underestimating any benefit associated with macrolide use, we also chose to specifically compare only patients treated with guideline-concordant therapies (as per IDSA/ATS)—macrolide/beta-lactam combinations vs respiratory fluoroquinolone monotherapy—in a secondary analysis [3]. Analyses were conducted using RevMan version 5.1 (The Nordic Cochrane Centre) and Comprehensive Meta-analysis version 2 (Biostat).

Funding sources played no role in study design; in the collection, analysis, and interpretation of data; in the writing of the manuscript; and in the decision to submit the manuscript for publication.

**RESULTS**

**Study Selection**

Our search returned 2834 citations from biomedical databases, 499 references from conference proceedings, 3 ongoing trials, and 3 hand-searched conference proceedings for a total of 2362 citations after duplicate removal. After screening all titles and/or abstracts, 58 studies were identified for full text review. Thirty-five studies were subsequently excluded for the following reasons: inappropriate or no comparison arm (n = 16), outpatient or intensive care unit patients (n = 12), missing mortality data (n = 4), same database as studies already included (n = 2), and study in progress (n = 1). Twenty-three full-text publications were included in our review [2, 17–38], including 18 observational cohort studies [2, 17–24, 26–31, 33, 34, 38] and 5 RCTs [25, 32, 35–37] (Figure 1).

![Flow diagram of study selection process](http://cid.oxfordjournals.org/)

**Figure 1.** Flow diagram of study selection process. Abbreviation: ICU, intensive care unit.
### Table 1. Study Characteristics

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Source</th>
<th>Location</th>
<th>Study Period</th>
<th>Study Sample Size</th>
<th>Disease Severity (mean PSI; proportion class 4/5)</th>
<th>Mean Age</th>
<th>Risk of Bias (Ottawa–Newcastle score)</th>
<th>Macrolide(s) Used</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCT</td>
<td>Lin (2007)† [17]</td>
<td>Taiwan single center</td>
<td>2004–06</td>
<td>50</td>
<td>79%; 70%</td>
<td>68</td>
<td>Low</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Zéros (2004) [37]</td>
<td>International multicenter</td>
<td>2001–02</td>
<td>212</td>
<td>98; 59%</td>
<td>72</td>
<td>High</td>
<td>Azithromycin</td>
</tr>
<tr>
<td>Cohort</td>
<td>Arnold (2009)† [17]</td>
<td>International multicenter</td>
<td>2001–07</td>
<td>1725</td>
<td>89; NR</td>
<td>67</td>
<td>Low (8)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Blasi (2008) [18]</td>
<td>Italian multicenter</td>
<td>2001–02 and 2003–04</td>
<td>2847</td>
<td>124; 100%</td>
<td>79</td>
<td>Low (8)</td>
<td>Azithromycin Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Dambrava (2008)† [22]</td>
<td>Spain single center</td>
<td>2001–04</td>
<td>571</td>
<td>NR; 80%</td>
<td>68</td>
<td>Low (8)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>McCabe (2009)† [28]</td>
<td>United States multicenter</td>
<td>1999–2003</td>
<td>57368</td>
<td>NR; 73%</td>
<td>71</td>
<td>Low (8)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Menendez (2002) [29]</td>
<td>Spain single center</td>
<td>1998–99</td>
<td>295</td>
<td>NR; 51%</td>
<td>70</td>
<td>Low (8)</td>
<td>NR</td>
</tr>
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<td>Menendez (2005)† [30]</td>
<td>Spain multicenter</td>
<td>2000–01</td>
<td>1295</td>
<td>89; 45%</td>
<td>66</td>
<td>Low (8)</td>
<td>NR</td>
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<tr>
<td></td>
<td>Menendez (2012)†,‡ [38]</td>
<td>Spain multicenter</td>
<td>2005–07</td>
<td>4043</td>
<td>NA; 47%</td>
<td>67</td>
<td>NA</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td>Minhas (2007)† [31]</td>
<td>Canada single center</td>
<td>2002–05</td>
<td>55</td>
<td>NR; 54%</td>
<td>68</td>
<td>Low (8)</td>
<td>Azithromycin Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Querol-Ribelles (2005) [33]</td>
<td>Spain single center</td>
<td>2000–03</td>
<td>459</td>
<td>107; 68%</td>
<td>71</td>
<td>Low (8)</td>
<td>Clarithromycin</td>
</tr>
<tr>
<td></td>
<td>Reyes-Calzada (2007) [34]</td>
<td>Spain multicenter</td>
<td>NR</td>
<td>425</td>
<td>NR; 59%</td>
<td>69</td>
<td>Low (8)</td>
<td>Azithromycin Clarithromycin Erythromycin</td>
</tr>
</tbody>
</table>

Abbreviations: NR, not reported; NA, not available; PSI, pneumonia severity index; RCT, randomized control trial.

† Unpublished data used.
‡ Characteristics for clinically evaluable population only.
‡‡ In press.
Study Characteristics
Twenty-three full text publications were included in our review, including 18 observational cohort studies and 5 RCTs. Unpublished data were sought from >50 authors and obtained for 11 studies—9 observational studies and 2 RCTs [17, 19, 20, 22, 25, 26, 30, 31, 36, 38]. Study and patient characteristics can be found in Table 1. Azithromycin, clarithromycin, and erythromycin were used in all studies, except 1 in which roxithromycin was used [32].

Quality Assessment
Our quality assessment can be found in Table 1. We assigned a low risk of bias to 3 RCTs despite their open-label design because the lack of blinding would be unlikely to affect mortality. We assigned an unclear risk of bias to 1 study [37] due to insufficient information regarding randomization and allocation. All cohort studies were considered high quality (Table 1).

Macrolide Treatment and Mortality
Among patients with pneumonia, macrolide use was associated with a statistically significant lower risk of mortality compared with nonmacrolide use (3.7% [1738 of 47 071 patients] vs 6.5% [5861 of 90 503]; RR, 0.78; 95% confidence interval [CI], .64–.95; P = .01) (Figure 2). There was considerable heterogeneity ($I^2 = 85\%$).

Macrolide/Beta-lactam Versus Respiratory Fluoroquinolone Subgroup and Mortality
The predefined subgroup analysis restricted exposure to only guideline-concordant regimens—specifically macrolide/beta-lactam combination therapies vs respiratory fluoroquinolone monotherapy—and thus included 16 studies and 12 624 patients (Table 1 and Figure 3). Within the guideline-concordant subgroup of patients, there was no effect on mortality according to antibiotic regimen (5.3% for macrolide/beta-lactam combinations [297 of 5574 patients] vs 5.8% for respiratory fluoroquinolones [436 of 7246]; RR, 1.17; 95% CI, .91–1.50; P = .22). Heterogeneity was moderate ($I^2 = 43\%$) but lower than in the primary analysis.

Exploring Potential Sources of Heterogeneity
Randomized Controlled Trials
All 5 of the RCTs included in our study compared macrolide/beta-lactam combinations with respiratory fluoroquinolones. Patients in RCTs were younger and had less severe disease (based on 2 studies that provided data) [25, 37] than patients in observational studies. Overall mortality in the RCTs was about 20% lower than in the observational studies (4.3% vs 5.5%). Comparing macrolide-based regimens with respiratory fluoroquinolones, no significant association with mortality was observed in the RCTs (4.6% [22 of 479] vs 4.1% [25 of 613];

Figure 2. Macrolide-based regimens versus nonmacrolide therapy and mortality: all included studies (N = 23). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
RR, 1.13; 95% CI, .65–1.98; P = .66) (Figure 4). No heterogeneity was observed (I² = 0%).

**Observational Studies**

Among the 18 observational studies included in our analysis (136,482 patients), the mean pneumonia severity index (PSI) score was available for 6 studies and ranged 101–124. Eight studies reported the proportion of patients with PSI class 4 or 5, and this ranged 51%–100%. Overall, recipients of macrolide-based regimens had statistically significantly lower mortality when compared with recipients of nonmacrolide-containing regimens (3.7% [1716 of 46,592 patients] vs 6.5% [5836 of 89,890]; RR, 0.75; 95% CI, .61–.92; P = .006) (Figure 5). Heterogeneity in this analysis was high (I² = 88%).

Three large studies using administrative databases and bereft of clinical information (ie, those based on claims data or ICD coding) were removed [20, 21, 28], leaving a sample size of 18,748 patients. With exclusion of these 3 studies, there was no longer an association between macrolide-based regimens and mortality (5.6% [358 of 6434 patients] vs 7.2% [889 of 12,314]; RR, 0.86; 95% CI, .69–1.07; P = .17), and heterogeneity was moderate (I² = 57%), although lower than in our main analysis (Figure 6).

Publication bias was not evident in any of our analyses (Egger’s test P value range, .07–.99, and no asymmetry on funnel plots), although the number of studies in the RCT sensitivity analysis was small.

**DISCUSSION**

In this systematic review and meta-analysis of over 135,000 patients hospitalized for CAP, we observed a statistically significant 22% relative decrease in mortality associated with the use of macrolide-based regimens when compared with nonmacrolide-containing regimens (RR, 0.78; 95% CI, .64–.95). There were, however, high levels of heterogeneity when...
pooling these studies ($I^2 > 75\%$ in most analyses), and most of this heterogeneity could not be easily explained. Of note, when analyses were restricted to patients treated with guideline-concordant regimens only (i.e., the comparator group was respiratory fluoroquinolones rather than any nonmacrolide-based regimen and macrolides were used in combination with beta-lactams), macrolide-based regimens appeared to offer no clinical advantage and the heterogeneity of these analyses was

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
Study or Subgroup & Macrolide Events & Total & Non-macrolide Events & Total & Weight & Risk Ratio M-H, Random, 95\% CI \\
\hline
Arnold 2009 [17] & 44 & 500 & 100 & 833 & 7.3% & 0.73 (0.52–1.03) \\
Asadi 2012 [2] & 48 & 556 & 273 & 2647 & 7.7% & 0.84 (0.62–1.12) \\
Blasi 2008 [18] & 47 & 559 & 166 & 1193 & 7.5% & 0.60 (0.44–0.82) \\
Brandenburg 2000 [19] & 1 & 49 & 3 & 83 & 0.8% & 0.56 (0.06–5.28) \\
Bratzler 2008 [20] & 374 & 6851 & 942 & 12542 & 8.8% & 0.73 (0.65–8.2) \\
Brown 2003 [21] & 559 & 22368 & 1328 & 22078 & 8.9% & 0.41 (0.37–0.45) \\
Dambrava 2008 [22] & 7 & 373 & 15 & 198 & 3.4% & 0.25 (0.10–0.60) \\
Frei 2003 [23] & 17 & 872 & 46 & 1581 & 5.5% & 0.67 (0.39–1.16) \\
Frei 2006 [24] & 3 & 255 & 18 & 255 & 2.2% & 0.17 (0.05–0.56) \\
Lodise 2007 [29] & 14 & 240 & 19 & 227 & 5.5% & 0.70 (0.36–1.36) \\
Marass 2007 [27] & 18 & 122 & 43 & 591 & 6.9% & 1.86 (1.11–3.10) \\
McCabe 2009 [28] & 19 & 194 & 12 & 101 & 4.5% & 0.82 (0.42–1.63) \\
Mendes 2005 [30] & 24 & 598 & 27 & 697 & 5.6% & 1.04 (0.60–1.78) \\
Mendes 2012 [31] & 44 & 1128 & 110 & 2915 & 7.2% & 1.03 (0.73–1.46) \\
Querol-Ribelles 2005 [33] & 25 & 209 & 15 & 250 & 5.0% & 1.99 (1.08–3.68) \\
Reyes-Calzada 2007 [34] & 21 & 276 & 14 & 149 & 4.8% & 0.81 (0.42–1.55) \\
\hline
Total (95% CI) & 46592 & 89890 & 100.0% & 0.75 (0.61–0.92) & & \\
\hline
Total events & 1716 & 5836 & & & & \\
Heterogeneity: $\chi^2 = 0.12, df = 17 (P < 0.0001); I^2 = 88\%$ \\
Test for overall effect: $Z = 2.72 (P = .006)$ \\
\end{tabular}
\caption{Macrolide-based regimens versus non-macrolide therapy and mortality: observational studies (n = 18). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.}
\end{table}

Figure 5. Macrolide-based regimens versus non-macrolide therapy and mortality: observational studies (n = 18). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

\begin{table}
\centering
\begin{tabular}{|l|c|c|c|c|c|c|}
\hline
Study or Subgroup & Macrolide Events & Total & Non-macrolide Events & Total & Weight & Risk Ratio M-H, Random, 95\% CI \\
\hline
Arnold 2009 [17] & 44 & 500 & 100 & 833 & 8.9% & 0.73 (0.52–1.03) \\
Asadi 2012 [2] & 48 & 556 & 273 & 2647 & 9.4% & 0.84 (0.62–1.12) \\
Blasi 2008 [18] & 47 & 559 & 166 & 1193 & 9.2% & 0.60 (0.44–0.82) \\
Brandenburg 2000 [19] & 1 & 49 & 3 & 83 & 0.9% & 0.56 (0.06–5.28) \\
Dambrava 2008 [22] & 7 & 373 & 15 & 198 & 4.0% & 0.25 (0.10–0.60) \\
Frei 2003 [23] & 17 & 872 & 46 & 1581 & 6.6% & 0.67 (0.39–1.16) \\
Frei 2006 [24] & 3 & 255 & 18 & 255 & 2.5% & 0.17 (0.05–0.56) \\
Lin 2007 [25] & 0 & 24 & 1 & 26 & 0.5% & 0.36 (0.02–8.43) \\
Lodise 2007 [29] & 14 & 240 & 19 & 227 & 5.5% & 0.70 (0.36–1.36) \\
Marass 2007 [27] & 18 & 122 & 43 & 591 & 6.9% & 1.86 (1.11–3.10) \\
Mendes 2002 [20] & 19 & 194 & 12 & 101 & 5.4% & 0.82 (0.42–1.63) \\
Mendes 2005 [30] & 24 & 598 & 27 & 697 & 6.7% & 1.04 (0.60–1.78) \\
Mendes 2012 [31] & 44 & 1128 & 110 & 2915 & 8.8% & 1.03 (0.73–1.46) \\
Minhas 2007 [31] & 4 & 24 & 3 & 31 & 2.0% & 1.72 (0.43–6.98) \\
Porter 2005 [32] & 7 & 175 & 6 & 174 & 3.0% & 1.16 (0.40–3.38) \\
Querol-Ribelles 2005 [33] & 25 & 209 & 15 & 250 & 6.0% & 1.99 (1.08–3.68) \\
Reyes-Calzada 2007 [34] & 21 & 276 & 14 & 149 & 5.7% & 0.81 (0.42–1.55) \\
Romanelli 2002 [35] & 7 & 101 & 7 & 103 & 3.3% & 1.02 (0.37–2.80) \\
Welte 2005 [36] & 5 & 77 & 6 & 200 & 2.7% & 2.16 (0.68–6.89) \\
Zervos 2004 [37] & 3 & 102 & 5 & 110 & 2.0% & 0.65 (0.16–2.64) \\
\hline
Total (95% CI) & 6434 & 12314 & 100.0% & 0.86 (0.69–1.07) & & \\
\hline
Total events & 358 & 889 & & & & \\
Heterogeneity: $\chi^2 = 43.79, df = 19 (P = .001); I^2 = 57\%$ \\
Test for overall effect: $Z = 1.36 (P = .17)$ \\
\end{tabular}
\caption{Macrolide-based regimens versus non-macrolide therapy and mortality: excluding administrative database studies (n = 20). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.}
\end{table}

Figure 6. Macrolide-based regimens versus non-macrolide therapy and mortality: excluding administrative database studies (n = 20). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.
much reduced ($I^2 = 43\%$). The only subgroup analysis associated with no heterogeneity was the analysis of RCTs, in which macrolide-based regimens were also not associated with mortality.

Issues related to observational studies vs trials, heterogeneity, and the suitability for pooling aside, there could be several potential reasons for the observed mortality benefit in our primary pooled analysis. First, the anti-inflammatory and immunomodulatory effects of macrolides may decrease or attenuate the inflammatory response due to CAP. Macrolides have been shown to decrease proinflammatory cytokines (tumor necrosis factor $\alpha$ [TNF-$\alpha$], interleukin 1, interleukin 6 [IL-6], interleukin 8 [IL-8], and interferon $\gamma$), neutrophil chemotaxis and adhesion, and oxidative metabolism [39]. In addition, they may inhibit microbial virulence factors such as biofilm formation and decrease mucus hypersecretion, leading to improved mucociliary clearance [39]. A review of the immunomodulatory effects of macrolides in CAP specifically found that acute inflammation could be attenuated by the effect of macrolides on cytokines, inflammatory cells, and structural cells [8]. Additionally, in a randomized controlled trial of patients with ventilator-associated pneumonia and sepsis, the addition of clarithromycin accelerated the resolution of pneumonia, hastened weaning from mechanical ventilation, and delayed death—all presumably due to immune modulation given the limited antimicrobial effect in this very specific patient population [40].

However, less well-known respiratory fluoroquinolones also exhibit immunomodulatory properties, such as reduction of proinflammatory cytokine levels and inhibition of secretion of TNF-$\alpha$, IL-6, and IL-8 [41]. These properties may explain why we observed no mortality benefit with macrolide-based regimens in analyses where the comparator was guideline-concordant regimens or fluoroquinolones.

Second, and we believe more likely, the association with reduced mortality may be a result of confounding, in particular confounding by indication. Previous studies have demonstrated that patients who received macrolides tended to be younger and have less severe disease compared with those treated with alternate agents [2]. We were unable to perform a direct comparison of mean age and PSI by antimicrobial therapy because many of the studies in our analysis either did not provide this data or only provided it for the patient population as a whole (not specifically for each antimicrobial subgroup).

Lastly, the marked heterogeneity observed suggests our patient populations and/or interventions were not necessarily comparable. Potential sources of heterogeneity that could not be adequately explored included differences in therapy (type of macrolide, dose, and duration), acute disease severity, and comorbid disease burden. Perhaps most important, however, were the antibiotic regimens constituting the comparison group. In fact, when analyses were restricted to RCTs or to subgroups that received guideline-concordant antibiotics (both situations that make the control comparison groups more uniform), we noted that heterogeneity diminished substantially and that macrolide-based regimens were no longer associated with pneumonia-related mortality.

Although our study has several strengths, we also acknowledge several limitations. First and foremost, we pooled observational studies with RCTs, and we undertook meta-analysis in spite of very high levels of heterogeneity. That said, we strongly believed that meta-analysis or review restricted to RCTs would not be sufficiently informative, especially given that only 1092 of 137,574 (0.8%) of the patients studied were from RCTs and RCTs constituted only 5 of 23 (22%) of the studies. Second, we excluded 8 studies not reported in English. Third, we included multiple sources of gray literature—unpublished data that has not been subjected to the peer review process. In fact, we believe this approach should be considered a strength because it allowed us to obtain additional data and reduce publication bias. That said, none of our analyses suggested important publication bias. Finally, few of the papers provided detailed microbiologic information regarding the etiology of CAP, and even fewer papers were able to provide information on the prevalence of drug-resistant $S. \ pneumoniae$.

In conclusion, although our overall results suggest a benefit for macrolide-based treatment in patients with pneumonia, analyses restricted to RCTs or to patients who received guideline-concordant regimens (with substantially less heterogeneity than in our overall analysis) attenuated, if not abolished, this mortality benefit. Our results suggest that if macrolides offer any clinical advantage it is very small or non-existent. Overall, our findings do support current guideline recommendations for empiric treatment that covers both typical and atypical pathogens but also illustrate there is more than sufficient equipoise to support the need for active-comparator randomized trials to determine the best treatment options for this very common condition.

**Supplementary Data**

Supplementary materials are available at Clinical Infectious Diseases online (http://www.oxfordjournals.org/our_journals/cid). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

**Notes**

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36. Welte T, Petermann W, Schurmann D, Bauer TT, Reimnitz P. Treatment with sequential intravenous or oral moxifloxacin was associated with faster clinical improvement than was standard therapy for hospitalized patients with community-acquired pneumonia who received initial parenteral therapy. Clin Infect Dis 2005; 41:1697–705.


