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, .65–1.98; $P = .66$; $I^2 = 0\%$) 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.

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Community acquired pneumonia (CAP), combined with influenza, is the eighth leading cause of death in Canada and the United States and the leading cause of hospitalization due to an infectious disease [1, 2]. For patients hospitalized with CAP, 30-day mortality rates are as high as 23% [1] and annual expenditures are $8–$10 billion in the United States alone [3]. Some previous studies have shown reduced morbidity and mortality in CAP patients treated with macrolide-based

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 pan-bronchiolitis [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*, *Chlamydophila* 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 $\leq$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 ($\leq$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).

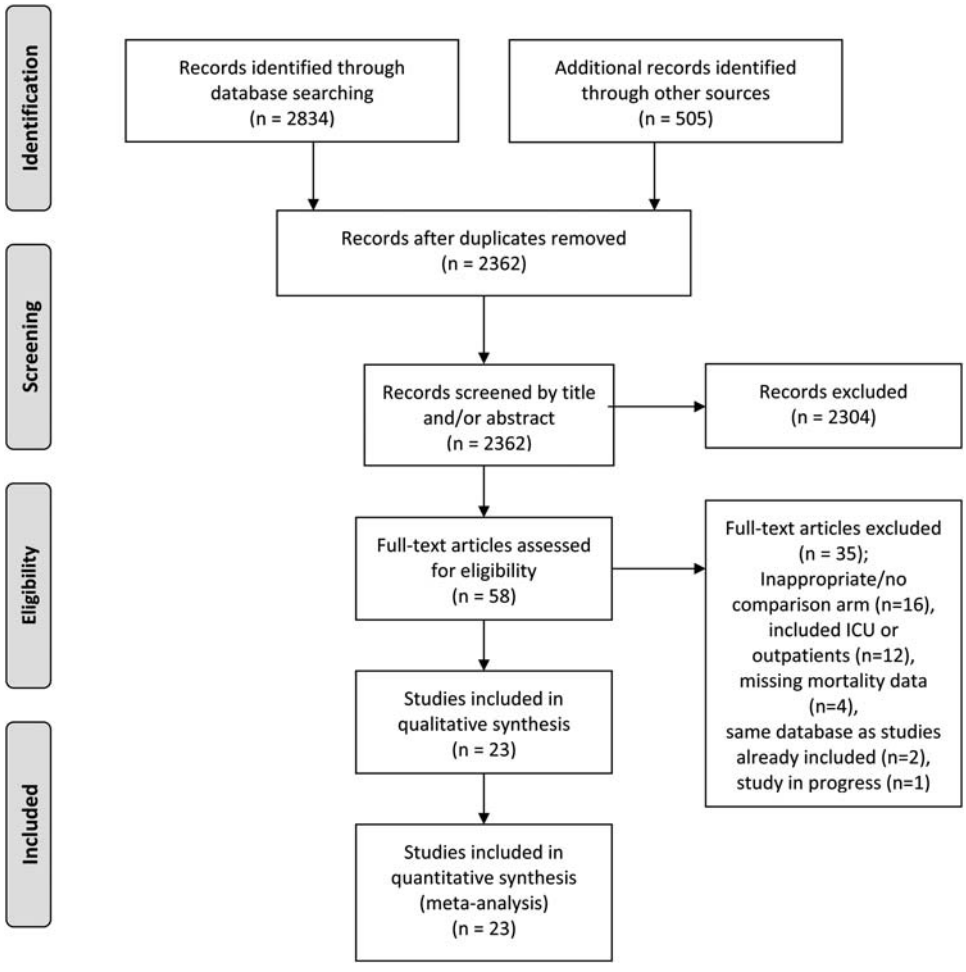

Figure 1. Flow diagram of study selection process. Abbreviation: ICU, intensive care unit.

Table 1. Study Characteristics

Study Design	Source	Location	Study Period	Study Sample Size	Disease Severity (mean PSI; proportion class 4/5)	Mean Age	Risk of Bias (Ottawa–Newcastle score)	Macrolide(s) Used
RCT	Lin (2007)[a] [17]	Taiwan single center	2004 – 06	50	79[b]; 70%	68	Low	Clarithromycin
	Portier (2005) [32]	France multicenter	2001 – 02	349	NR	61	Low	Roxithromycin
	Romanelli (2002) [35]	Italy multicenter	1997 – 2001	206	NR	75	Unclear	Clarithromycin
	Welte (2005) [36]	European multicenter	2001 – 03	323	NR	NR	Low	Erythromycin
	Zervos (2004) [37]	International multicenter	2001 – 02	212	98; 59%	72	High	Azithromycin
Cohort	Arnold (2009)[a] [17]	International multicenter	2001 – 07	1725	89; NR	67	Low (8)	NR
	Asadi (2012)[a,c] [2]	Canada multicenter	2000 – 02	3203	103; 63%	69	Low (8)	Azithromycin Clarithromycin Erythromycin
	Blasi (2008) [18]	Italian multicenter	2001 – 02 and 2003 – 04	2847	124; 100%	79	Low (8)	Azithromycin Clarithromycin
	Brandenburg (2000)[a] [19]	International (North America) multicenter	1991 – 94	132	NR; 41%	59	Low (8)	Erythromycin
	Bratzler (2008)[a] [20]	United States multicenter	1998 – 2001	19 393	NR	NR	Low (8)	NR
	Brown (2003) [21]	United States multicenter	1997 – 99	44 814	NR		Low (7)	NR
	Dambrava (2008)[a] [22]	Spain single center	2001 – 04	571	NR; 80%	68	Low (8)	NR
	Frei (2003) [23]	United States multicenter (USCAP database)	1997 – 01	2453	NR	70 ± 17	Low (8)	Azithromycin Clarithromycin Erythromycin
	Frei (2006) [24]	United States multicenter	1999 – 2001	631	106; 65%	73	Low (8)	Azithromycin Clarithromycin Erythromycin
	Lodise (2007)[a] [26]	United States multicenter	1999 – 2003	467	NR		Low (8)	Azithromycin
	Marass (2004) [27]	Canada multicenter	1997 – 2000	698	116; 74%	78	Low (8)	NR
	McCabe (2009)[a] [28]	United States multicenter	1999 – 2003	57 368	NR; 73%	71	Low (8)	NR
	Menendez (2002) [29]	Spain single center	1998 – 99	295	NR; 51%	70	Low (8)	NR
	Menendez (2005)[a] [30]	Spain multicenter	2000 – 01	1295	89; 45%	66	Low (8)	NR
	Menendez (2012)[a,c] [38]	Spain multicenter	2005 – 07	4043	NA; 47%	67	NA	NR
	Minhas (2007)[a] [31]	Canada single center	2002 – 05	55	NR; 54%	68	Low (8)	Azithromycin Clarithromycin
	Querol-Ribelles (2005) [33]	Spain single center	2000 – 03	459	107; 68%	71	Low (8)	Clarithromycin
	Reyes-Calzada (2007) [34]	Spain multicenter	NR	425	NR; 59%	69	Low (8)	Azithromycin Clarithromycin Erythromycin

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

[a] Unpublished data used.

[b] Characteristics for clinically evaluable population only.

[c] 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% [5861of 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 fluoquinolones, no significant association with mortality was observed in the RCTs (4.6% [22 of 479] vs 4.1% [25 of 613];

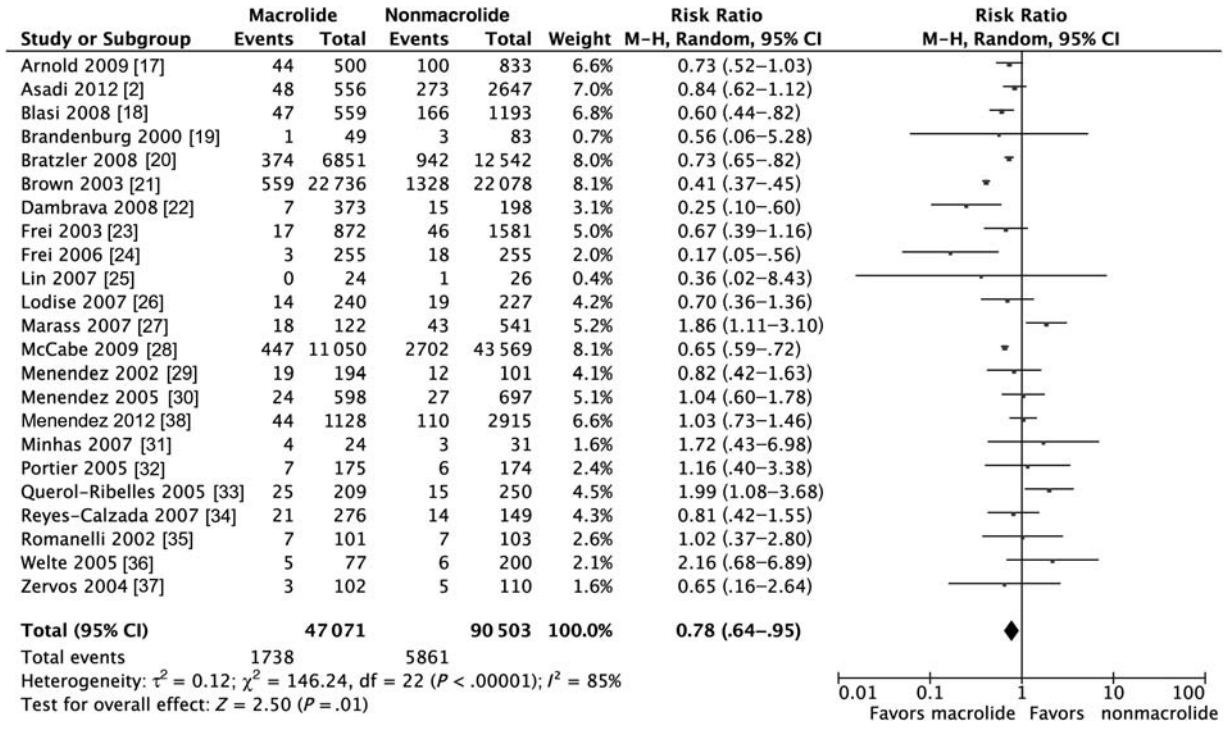

Figure 2. Macrolide-based regimens versus nonmacrolide therapy and mortality: all included studies (N = 23). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

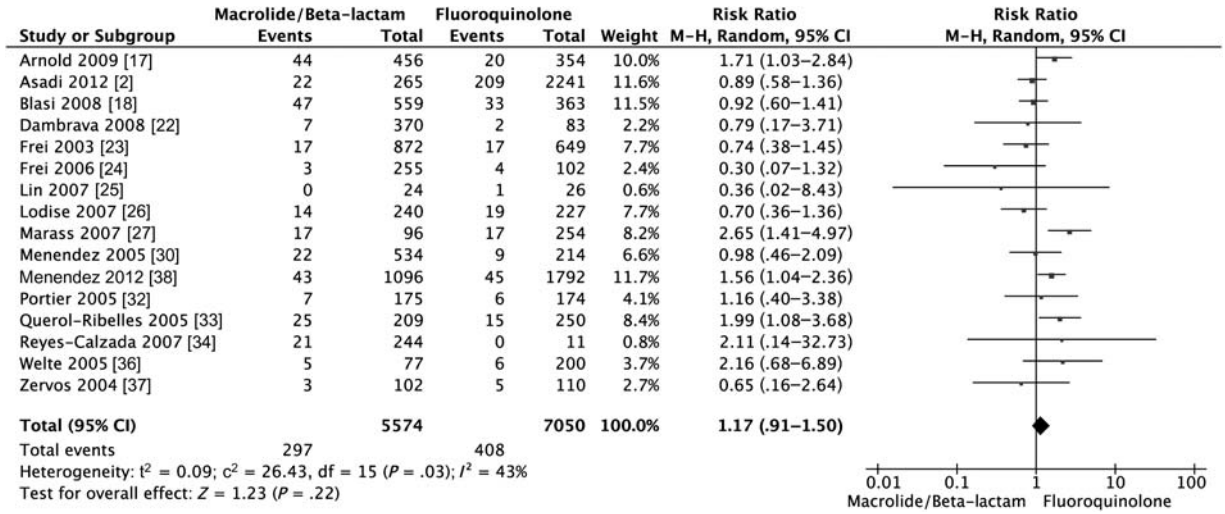

Figure 3. Guideline-concordant macrolide/beta-lactam therapy versus respiratory fluoroquinolone monotherapy and mortality (n = 16). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

RR, 1.13; 95% CI, .65–1.98; $P = .66$) (Figure 4). No heterogeneity was observed ($I^2 = 0\%$).

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 ($I^2 = 88\%$).

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 ($I^2 = 57\%$), 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 non-macrolide-containing regimens (RR, 0.78; 95% CI, .64–.95). There were, however, high levels of heterogeneity when

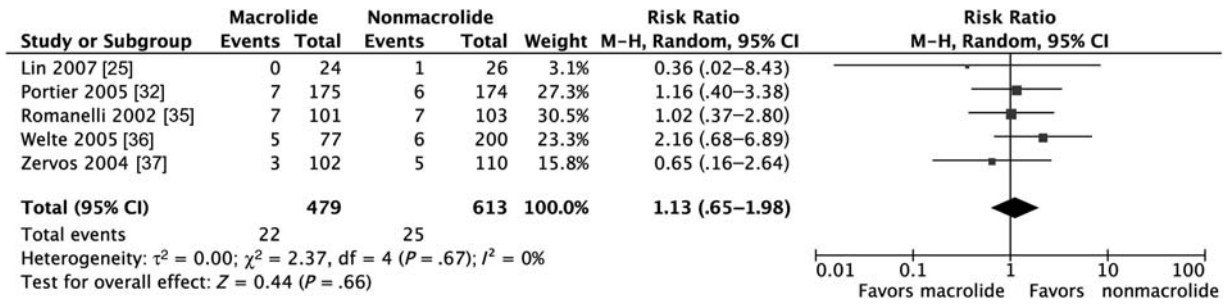

Figure 4. Macrolide-based regimens versus non-macrolide therapy and mortality: randomized controlled trials (n = 5). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

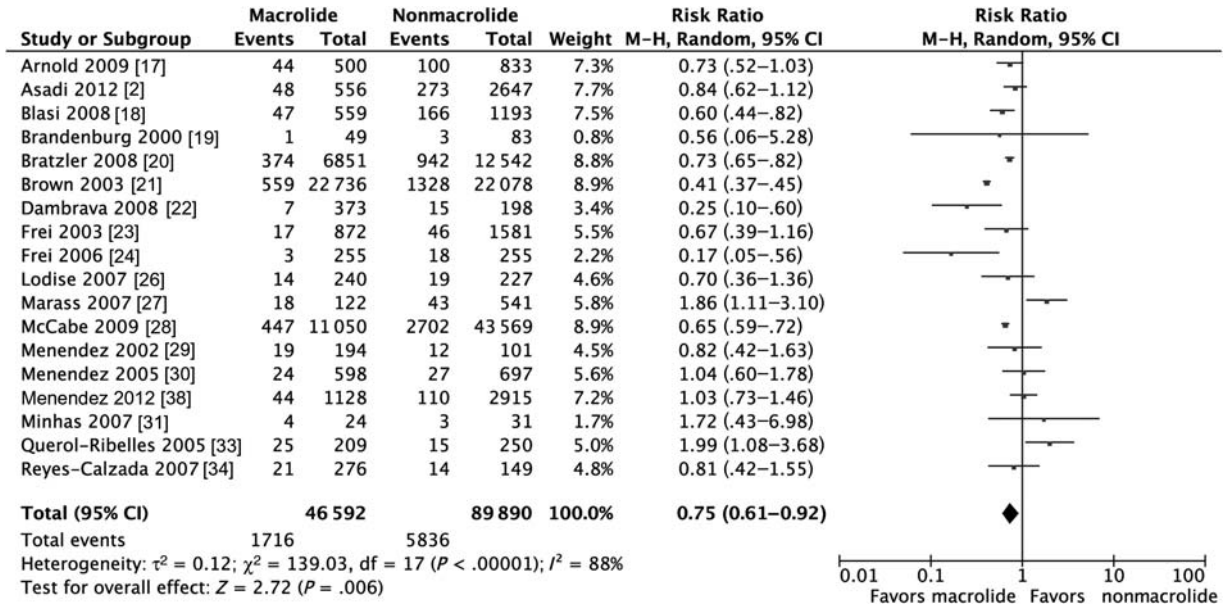

Figure 5. Macrolide-based regimens versus non-macrolide therapy and mortality: observational studies (n = 18). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

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 (ie, the comparator group was respiratory fluoroquinolones rather than any nonmacrolid-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

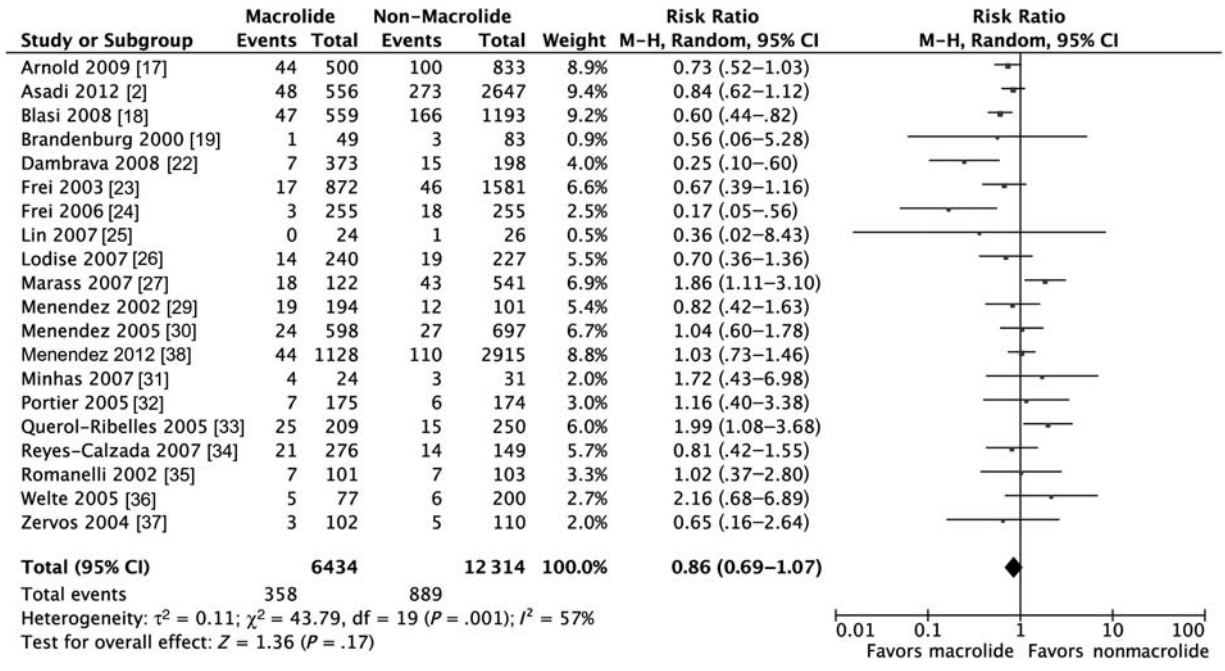

Figure 6. Macrolide-based regimens versus non-macrolide therapy and mortality: excluding administrative database studies (n = 20). Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

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 α [TNF-α], interleukin 1, interleukin 6 [IL-6], interleukin 8 [IL-8], and interferon γ), 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-a, 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 respiratory 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 nonexistent. 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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W. I. S. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the analysis. All authors participated in study conception, design, interpretation, critical revisions, and approved the final manuscript. L. A. and W. I. S. undertook data abstraction and analyses and drafted the initial manuscript. S. R. M., D. T. E., and T. J. M. obtained funding and supervised the study. All authors have seen and approved the final version. S. R. M. will act as the guarantor.

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Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med **2010**; 122:130–41.
2. Asadi L, Eurich DT, Gamble JM, Minhas-Sandhu JK, Marrie TJ, Majumdar SR. Impact of guideline-concordant antibiotics and macrolide/B-lactam combinations in 3203 patients hospitalized with pneumonia: prospective cohort study [published online ahead of print 8 March 2012]. Clin Microbiol Infect **2012**; doi:10.1111/j.1469-0691.2012.03783.x.
3. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis **2007**; 44(Suppl 2):S27–72.
4. Martinez JA, Horcajada JP, Almela M, et al. Addition of a macrolide to a beta-lactam-based empirical antibiotic regimen is associated with lower in-hospital mortality for patients with bacteremic pneumococcal pneumonia. Clin Infect Dis **2003**; 36:389–95.
5. Metersky ML, Ma A, Houck PM, Bratzler DW. Antibiotics for bacteremic pneumonia: improved outcomes with macrolides but not fluoroquinolones. Chest **2007**; 131:466–73.
6. Restrepo MI, Mortensen EM, Waterer GW, Wunderink RG, Coalson JJAnzueto A. Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. Eur Respir J **2009**; 33:153–9.
7. Zarogoulidis P, Papanas N, Kioumis I, Chatzaki E, Maltezos E, Zarogoulidis K. Macrolides: from in vitro anti-inflammatory and immunomodulatory properties to clinical practice in respiratory diseases [published online ahead of print 22 November 2011]. Eur J Clin Pharmacol **2011**.
8. Amsden GW. Anti-inflammatory effects of macrolides—an underappreciated benefit in the treatment of community-acquired respiratory tract infections and chronic inflammatory pulmonary conditions? J Antimicrob Chemother **2005**; 55:10–21.
9. Kudoh S, Azuma A, Yamamoto M, Izumi T, Ando M. Improvement of survival in patients with diffuse panbronchiolitis treated with low-dose erythromycin. Am J Respir Crit Care Med **1998**; 157(6 Pt 1): 1829–32.
10. Gottlieb J, Szangolies J, Koehnlein T, Golpon H, Simon A, Welte T. Long-term azithromycin for bronchiolitis obliterans syndrome after lung transplantation. Transplantation **2008**; 85:36–41.
11. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Sapsford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med **2008**; 178:1139–47.
12. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. BMJ **2009**; 339:b2535.
13. Glanville JM, Lefebvre C, Miles JN, Camosso-Stefinovic J. How to identify randomized controlled trials in MEDLINE: ten years on. J Med Libr Assoc **2006**; 94:130–6.
14. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane collaboration's tool for assessing risk of bias in randomised trials [published online ahead of print 18 October 2011]. BMJ **2011**; 343:d5928.
15. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. Available at: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 3 August 2011.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ **1997**; 315:629–34.
17. Arnold FW, LaJoie AS, Brock GN, et al. Improving outcomes in elderly patients with community-acquired pneumonia by adhering to national guidelines: Community-Acquired Pneumonia Organization International cohort study results. Arch Intern Med **2009**; 169:1515–24.
18. Blasi F, Iori I, Bulfoni A, Corrao S, Costantino S, Legnani D. Can CAP guideline adherence improve patient outcome in internal medicine departments? Eur Respir J **2008**; 32:902–10.
19. Brandenburg JA, Marrie TJ, Coley CM, et al. Clinical presentation, processes and outcomes of care for patients with pneumococcal pneumonia. J Gen Intern Med **2000**; 15:638–46.
20. Bratzler DW, Ma A, Nsa W. Initial antibiotic selection and patient outcomes: observations from the National Pneumonia Project. Clin Infect Dis **2008**; 47(Suppl 3):S193–201.
21. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. Chest **2003**; 123:1503–11.
22. Dambrava PG, Torres A, Valles X, et al. Adherence to guidelines' empirical antibiotic recommendations and community-acquired pneumonia outcome. Eur Respir J **2008**; 32:892–901.
23. Frei CR, Koeller JM, Burgess DS, Talbert RL, Johnsrud MT. Impact of atypical coverage for patients with community-acquired pneumonia managed on the medical ward: results from the United States Community-Acquired Pneumonia Project. Pharmacotherapy **2003**; 23:1167–74.
24. Frei CR, Restrepo MI, Mortensen EM, Burgess DS. Impact of guideline-concordant empiric antibiotic therapy in community-acquired pneumonia. Am J Med **2006**; 119:865–71.
25. Lin TY, Lin SM, Chen HC, et al. An open-label, randomized comparison of levofloxacin and amoxicillin/clavulanate plus clarithromycin for the treatment of hospitalized patients with community-acquired pneumonia. Chang Gung Med J **2007**; 30:321–32.
26. Lodise TP, Kwa A, Cosler L, Gupta R, Smith RP. Comparison of beta-lactam and macrolide combination therapy versus fluoroquinolone monotherapy in hospitalized Veterans Affairs patients with community-acquired pneumonia. Antimicrob Agents Chemother **2007**; 51:3977–82.
27. Marras TK, Jamieson L, Chan CK. Inpatient care of community-acquired pneumonia: the effect of antimicrobial guidelines on clinical outcomes and drug costs in Canadian teaching hospitals. Can Respir J **2004**; 11:131–7.
28. McCabe C, Kirchner C, Zhang H, Daley J, Fisman DN. Guideline-concordant therapy and reduced mortality and length of stay in adults with community-acquired pneumonia: playing by the rules. Arch Intern Med **2009**; 169:1525–31.
29. Menendez R, Ferrando D, Valles JM, Vallterra J. Influence of deviation from guidelines on the outcome of community-acquired pneumonia. Chest **2002**; 122:612–7.

30. Menendez R, Torres A, Zalacain R, et al. Guidelines for the treatment of community-acquired pneumonia: predictors of adherence and outcome. Am J Respir Crit Care Med **2005**; 172:757–62.
31. Minhas R, Walker SAN, Rachlis A. Management of community-acquired pneumonia at a tertiary-care teaching hospital. Can J Hosp Pharm **2007**; 60:245–56.
32. Portier H, Brambilla C, Garre M, Paganin F, Poubeau P, Zuck P. Moxifloxacin monotherapy compared to amoxicillin-clavulanate plus roxithromycin for nonsevere community-acquired pneumonia in adults with risk factors. Eur J Clin Microbiol Infect Dis **2005**; 24: 367–76.
33. Querol-Ribelles JM, Tenias JM, Querol-Borras JM, et al. Levofloxacin versus ceftriaxone plus clarithromycin in the treatment of adults with community-acquired pneumonia requiring hospitalization. Int J Antimicrob Agents **2005**; 25:75–83.
34. Reyes Calzada S, Martinez Tomas R, Cremades Romero MJ, Martinez Moragon E, Soler Cataluna JJ, Menendez Villanueva R. Empiric treatment in hospitalized community-acquired pneumonia. Impact on mortality, length of stay and re-admission. Respir Med **2007**; 101:1909–15.
35. Romanelli G, Cravarezza P, Pozzi A, et al. Carbapenems in the treatment of severe community-acquired pneumonia in hospitalized elderly patients: a comparative study against standard therapy. J Chemother **2002**; 14:609–17.
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.
37. Zervos M, Mandell LA, Vrooman PS, et al. Comparative efficacies and tolerabilities of intravenous azithromycin plus ceftriaxone and intravenous levofloxacin with step-down oral therapy for hospitalized patients with moderate to severe community-acquired pneumonia. Treat Respir Med **2004**; 3:329–36.
38. Menendez R, Torres A, Reyes S, et al. Initial management of pneumonia and sepsis: factors associated with improved outcome. Eur Respir J **2012**; 39:156–62.
39. Healy DP. Macrolide immunomodulation of chronic respiratory diseases. Curr Infect Dis Rep **2007**; 9:7–13.
40. Giamarellos-Bourboulis EJ, Pechere JC, Routsi C, et al. Effect of clarithromycin in patients with sepsis and ventilator-associated pneumonia. Clin Infect Dis **2008**; 46:1157–64.
41. Dalhoff A. Immunomodulatory activities of fluoroquinolones. Infection **2005**; 33(Suppl 2):55–70.