anticoagulant treatment in patients sustaining SI-ALI. Nonetheless, the work of Miller et al (12) advances our knowledge of the promise of this approach and its potential translation to other disease entities.

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Macrolides and Mortality in Severe Community-Acquired Pneumonia*

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Community-acquired pneumonia remains one of the leading indications for ICU admission internationally, with 5–15% of hospitalized cases resulting in ICU admission (1). The causative pathogen is rarely known at admission, and so antibiotic prescribing is empirical, directed at the organisms most likely to be responsible based on epidemiological data.

The likely causative organisms in an ICU context are well described and include the most common pathogen, *Streptococcus pneumoniae* along with *Staphylococcus aureus*, *Legionella pneumophila*, and Gram-negative organisms. Some organisms particularly the atypical pathogens *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, viruses, and the typical pathogen *Haemophilus influenzae* are apparently less common in an ICU context but are still prevalent (2, 3).

*See also p. 420.

Key Words: antibiotics; inflammation; intensive care; meta-analysis; pneumonia

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With knowledge of these likely pathogens, guidelines from the Infectious Disease Society of America/American Thoracic Society, the British Thoracic Society, and others internationally recommend a combination of β-lactam antibiotics, which have activity against "typical" pneumonia pathogens and an agent with activity against atypical pathogens, such as a macrolide or fluoroquinolone (3–5).

Due to an absence of randomized controlled trials (RCTs) in this area, there is no firm evidence of superiority for any of the recommended antibiotic regimes, and guidelines are based on a combination of observational evidence and expert opinion (3, 4).

In this issue of *Critical Care Medicine*, Sligl et al (6) present a meta-analysis of observational studies comparing mortality in patients treated with macrolide-containing regimes and regimes not containing a macrolide (including fluoroquinolone-containing regimes and those providing no "atypical" antibiotic coverage). This analysis is an impressive achievement, as no previous studies have been able to specifically evaluate the performance of macrolides in the ICU-admitted population, and this was achieved by obtaining large amounts of unpublished data, in a systematic way, from the authors of the original publications.

Sligl et al (6) report a 3% absolute (18% relative) reduction in mortality with macrolide-containing regimes. This difference persisted when excluding patients treated with macrolide monotherapy, but the authors found no statistically significant difference comparing β-lactam macrolide versus β-lactam and fluoroquinolone combinations (6).

A survival advantage of macrolides is appealing and plausible, as in addition to their known antimicrobial activity, macrolides have immunomodulatory effects attributed to their 14

and 15 member lactone rings. The clinical evidence of this is classically demonstrated in diffuse panbronchiolitis but also in cystic fibrosis and non-cystic fibrosis bronchiectasis where macrolides have demonstrated benefits that appear to go beyond their antimicrobial activity (7).

Meta-analyses are, however, always subject to the limitations of their constituent studies. In the analysis by Sligl et al (6), several factors limit enthusiasm for the findings. All included studies were observational cohorts. Of 28 included studies, 15 studies were retrospective and most demonstrated baseline differences (such as lower age or severity of disease) in the macrolide-treated patients versus the comparator (6). Although the authors admirably tried to pool adjusted effect estimates, only nine studies reported adjusted data.

In prospective studies, the authors did not observe a benefit of macrolide versus nonmacrolide-containing regimes (24% vs 23%). This evidence mirrored the findings of a previous meta-analysis of macrolide-containing regimes in ward patients from the same group. In that analysis, the "raw" data suggested a benefit of macrolides, but after excluding three large administrative database studies that accounted for 86% of the included patients, macrolide-containing regimes were no longer significantly associated with a mortality benefit (risk ratio [RR], 0.86; 95% CI, 0.69–1.07; $p = 0.2$) (8). These data suggest that the mortality benefit reported with macrolides, both in ward patients and ICU-admitted patients, is largely driven by lower quality retrospective studies which may be more prone to bias and confounding (8).

Although the authors infer a trend toward benefit when comparing β-lactam macrolide regimes with those containing fluoroquinolones, the differences were not statistically significant and it cannot be stated, even in this analysis, that macrolide-containing regimes are superior to fluoroquinolones. Fluoroquinolones, which also cover atypical pathogens, have been evaluated in multiple RCTs. These studies have been consolidated in a Cochrane review and meta-analysis of 28 trials enrolling 5,939 patients (9). This analysis showed no benefit of empirical atypical coverage (RR, 1.14; 95% CI, 0.84–1.55). Furthermore, RCTs have been conducted comparing macrolide-containing regimes with fluoroquinolone-containing regimes. The results of these RCTs have found no benefit of macrolide with one meta-analysis showing superior results for fluoroquinolones compared with β-lactam/macrolide combinations in terms of treatment success (odds ratio, 1.39; 95% CI, 1.02–1.90) (10). Although not conducted in the critically ill population, these data strongly suggest that macrolide- and fluoroquinolone-containing regimes are equivalent in efficacy and would argue against a specific anti-inflammatory effect of macrolides leading to clinically important reductions in pneumonia mortality. The fact that regimes covering atypical pathogens are associated with a powerful reduction in mortality in observational studies but fail to demonstrate this in RCTs raises serious concerns about the reliability of observational data.

Macrolides are potent drivers of antibiotic resistance (11), and like fluoroquinolones, they are not without adverse effects. In addition to a high frequency of "minor" adverse events like gastrointestinal side effects, macrolides prolong the QT interval and have been repeatedly linked with an increase frequency of sudden cardiac death and cardiovascular events (12, 13).

The analysis by Sligl et al (6) was not able to evaluate the prevalence of nonfatal adverse events in macrolide-treated patients, nor was there any data on important nonfatal endpoints such as ICU length of stay, duration of mechanical ventilation, long-term outcomes, and quality of life. Such data are only ever likely to emerge from a well-conducted randomized trial.

So where does this leave us? Macrolide-containing regimes have a clear, statistically significant mortality advantage compared with nonmacrolide-containing regimes in predominantly retrospective observational cohort studies but not in prospective cohort studies. Macrolides do not demonstrate a statistically significant mortality advantage over fluoroquinolone regimes, either in the observational studies or in RCTs (6–9).

The findings therefore broadly support international guideline recommendations to use β-lactam macrolide or fluoroquinolone combination treatment in severe community-acquired pneumonia.

Sligl et al (6), rightly in my view, call for a moratorium on observational studies of macrolides in community-acquired pneumonia. It is clear from this analysis that we have enough observational data and that only randomized studies will provide the answers we now need on macrolide efficacy.

While awaiting a definitive RCT, doctors should follow national guidelines.

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Macrolides and Mortality in Critically Ill Patients With Community-Acquired Pneumonia: A Systematic Review and Meta-Analysis*

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Objective: Some studies suggest better outcomes with macrolide therapy for critically ill patients with community-acquired pneumonia. To further explore this, we performed a systematic review of studies with mortality endpoints that compared macrolide therapy with other regimens in critically ill patients with community-acquired pneumonia.

Data Sources: Studies were identified via electronic databases, grey literature, and conference proceedings through May 2013.

Study Selection: Using prespecified criteria, two reviewers selected studies; studies of outpatients and hospitalized noncritically ill patients were excluded.

Data Extraction: Two reviewers extracted data and evaluated bias using the Newcastle-Ottawa Scale. Random effects models were used to generate pooled risk ratios and evaluate heterogeneity (I^2).

Data Synthesis: Twenty-eight observational studies (no randomized control trials) were included. Average age ranged from 58 to 78 years and 14–49% were women. In our primary analysis of 9,850 patients, macrolide use was associated with statistically significant lower mortality compared with nonmacrolides (21% [846 of 4,036 patients] vs 24% [1,369 of 5,814]; risk ratio, 0.82; 95% CI, 0.70–0.97; $p = 0.02$; $I^2 = 63\%$). When macrolide monotherapy was excluded, the macrolide mortality benefit was maintained (21% [737 of 3,447 patients] vs 23% [1,245 of 5,425]; risk ratio, 0.84; 95% CI, 0.71–1.00; $p = 0.05$; $I^2 = 60\%$). When broadly guideline-concordant regimens were compared, there was a trend to improved mortality and heterogeneity was reduced (20% [511 of 2,561 patients] mortality with beta-lactam/macrolide therapy vs 23% [386 of 1,680] with beta-lactam/fluoroquinolone; risk ratio, 0.83; 95% CI, 0.67–1.03; $p = 0.09$; $I^2 = 25\%$). When adjusted risk estimates were pooled from eight studies, macrolide therapy was still associated with a significant reduction in mortality (risk ratio, 0.75; 95% CI, 0.58–0.96; $p = 0.02$; $I^2 = 57\%$).

Conclusions: In observational studies of almost 10,000 critically ill patients with community-acquired pneumonia, macrolide use was associated with a significant 18% relative (3% absolute) reduction in mortality compared with nonmacrolide therapies. After pooling data from studies that provided adjusted risk estimates, an even larger mortality reduction was observed. These results suggest that macrolides be considered first-line combination treatment in critically ill patients with community-acquired pneumonia and support current guidelines. (*Crit Care Med* 2014; 42:420–432)

Key Words: community-acquired pneumonia; critical care; intensive care; macrolide; mortality; systematic review

***See also p. 475.**

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Dr. Sligl 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 article. Drs. Sligl and Asadi undertook data abstraction. Dr. Sligl performed the analyses and drafted the initial article. Drs. Sligl, Eurich, Marrie, and Majumdar obtained funding, and Dr. Majumdar supervised the study. All authors have seen and approved the final version.

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Combined with influenza, community-acquired pneumonia (CAP) is the most frequent cause of infection-related death and the eighth leading cause of death overall in the United States (1, 2). Nearly half of all CAP patients require hospital admission (3, 4), and 10–20% have severe disease requiring ICU level of care (5). Morbidity and mortality in patients with severe CAP is high—up to 50% develop septic shock, 40–80% require mechanical ventilation, and mortality rates generally approach 20–50% (5).

Some studies suggest improved outcomes with macrolide therapy in patients with CAP, independent of antimicrobial effect—presumably due to immune modulation. For example, in both experimental and clinical sepsis, studies have demonstrated macrolide-induced leukocyte adhesion downregulation and decreased inflammatory cytokine production (6, 7). Indeed, the use of macrolides has been associated with improved outcomes not only in various chronic noninfectious pulmonary conditions (8–10) but also in pneumonia (11–15). Furthermore, it appears that the largest effects may exist in patients with more robust systemic inflammatory responses manifested as very severe disease (11) or shock (14). Most of these studies, however, are not randomized trials, and a recent meta-analysis of 23 studies (137,574 patients) we undertook did not demonstrate a mortality benefit with macrolide use in hospitalized CAP patients when restricted to trials or studies comparing guideline-concordant regimens (16). Furthermore, this analysis specifically excluded critically ill patients.

In addition to uncertain benefit, concerns regarding increasing macrolide resistance and the potential toxicities of therapy—specifically sudden death associated with QTc interval prolongation—have compelled physicians to reconsider the risk-benefit ratio. In fact, one recent study demonstrated an increase in risk of cardiovascular death in patients with upper respiratory infection who received azithromycin compared with those who received no antibiotics, amoxicillin, or fluoroquinolones (17).

Therefore, our aim was to systematically review and meta-analyze all available studies that examined the association between macrolide use and mortality in critically ill patients with CAP. We hypothesized if any immune modulatory benefit were to exist; it would be observed in this population given the high prevalence of systemic inflammation and septic shock.

MATERIALS AND METHODS

Data Sources and Searches

Our search strategy was created and carried out prior to the study selection. Meta-analysis Of Observational Studies in Epidemiology reporting guidelines and checklist were followed (18). A comprehensive search was conducted by an experienced librarian (L.T.) in the following key electronic biomedical databases, from inception through May 2013, 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 (19), in addition to study design filters from BMJ Clinical Evidence (20), was applied in Medline and Embase. All available years were searched without language restrictions. International Standard Randomized Controlled Trial Number Register and ClinicalTrials.gov were searched to identify studies in progress.

In addition to electronic databases, we hand searched the latest 3 years of conference proceedings from nine germane meetings, including the European Society of Intensive Care Medicine, European Respiratory Society, Infectious Diseases Society of America, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, Interscience Conference on Antimicrobial Agents and Chemotherapy, Critical Care Canada Forum, Society of Critical Care Medicine, and the European Congress of Microbiology and Infectious Diseases. We consulted content experts and contacted authors of studies who might have such data. We attempted up to three contacts with corresponding authors before considering them nonresponsive.

Study Selection

A checklist was used to assess whether studies met our inclusion criteria for population (critically ill adult patients with CAP; i.e., admitted to an ICU), exposure (macrolide antibiotic), comparison group (nonmacrolide antibiotic), outcome (in-hospital, ICU, 28- or 30-d mortality), and study design (randomized control trials and observational cohort studies). If multiple outcomes were reported we chose 28- or 30-day mortality (instead of in-hospital or ICU mortality). Duplicates, studies on outpatients or hospitalized noncritically ill (ward) patients, or patients with nosocomial pneumonia were excluded.

Data Extraction and Quality Assessment

Two trained reviewers independently conducted study selection, abstracted data, and assessed the risk of bias (W.I.S., L.A.). Discrepancies between reviewers were resolved through discussion and consensus; if consensus could not be obtained, discrepancies were resolved by S.R.M. Because there were no randomized trials in the analysis, we evaluated risk of bias using the Newcastle-Ottawa Scale, assigning a maximum of nine points to each study, with five or less points indicating a high risk of bias (21).

Data Synthesis and Analysis

Our primary analysis examined the effect of macrolide exposure on short-term (in-hospital, ICU, 28- or 30-d) mortality. Macrolide monotherapy or combination therapies were included and were compared with any/all nonmacrolide therapies. We tabulated 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). Each study was weighted by the inverse of the total variance comprising both the within study variance and the between study variance. Heterogeneity was assessed using the I^2 test statistic and classified as low (≤ 25%), moderate (> 25–50%), or high

(> 50%). We did not prespecify any I^2 that would preclude meta-analytic pooling. We considered a two-tailed *p* value of less than 0.05 to demonstrate statistical significance and *p* values between 0.05 and 0.10 to demonstrate a statistical "trend." Publication bias was assessed by visually inspecting funnel plots for asymmetry and applying the Egger test (22), with the results considered to indicate potential for publication bias when the *p* value is less than 0.05. Analyses were conducted using Review Manager (RevMan) Version 5·1 (The Nordic Cochrane Centre, Copenhagen, Denmark) and Comprehensive Meta-analysis Version 2, (Biostat, Englewood, NJ).

Potential sources of heterogeneity were considered a priori and appropriate subgroup analyses planned. First, we excluded patients who received macrolide monotherapy as these patients would be more likely to be younger and have less severe disease and as a result may have better outcomes due to confounding. Second, we chose to compare combination therapies that had similar antimicrobial spectra and were reasonable options for the treatment of patients with severe CAP—specifically beta-lactam/macrolide (BLM) versus beta-lactam/fluoroquinolone (BLF) therapies. Both of these regimens are broadly guideline-concordant although we were unable to perform a strict guideline-concordant versus discordant comparison given the complexity of Infectious Diseases Society of America/American Thoracic Society empiric therapy guidelines in critically ill patients (23). Third, we restricted our analysis only to prospective observational studies assuming that, by excluding retrospective studies, we might minimize bias and confounding. Fourth, we chose to examine patients with more severe disease defined by the need for mechanical ventilation. Fifth, we examined only patients presenting with septic shock (systolic blood pressure < 90 mm Hg or need for vasopressors after fluid replacement). Sixth, we examined patients with confirmed *Streptococcus pneumoniae*, the most common cause of severe CAP in North America. Last, as others have done (24) to minimize confounding, we pooled adjusted risk estimates using inverse variance weighting. To the degree that these studies would be better able to control confounding, we expected to see an attenuation of the estimate of effect and a bias to the null if the primary (unadjusted) results were a result of confounding.

RESULTS

Study Selection

Our search returned 5,526 citations and 20 conference proceedings for a total of 4,065 unique citations. After screening all titles and/or abstracts, 115 studies were identified for full-text review. Eighty-seven studies were subsequently excluded for the following reasons: ICU patients were excluded ($n = 25$) or not specified/subgrouped ($n = 26$), macrolide-specific data were not available ($n = 26$), mortality data were not given ($n = 2$), CAP cohort was not subgrouped ($n = 2$; e.g., patients with pneumococcal bacteremia but no primary site of infection data available), no comparison group ($n = 2$), and duplicates ($n = 4$), leaving 28 available for analysis (**Fig. 1**).

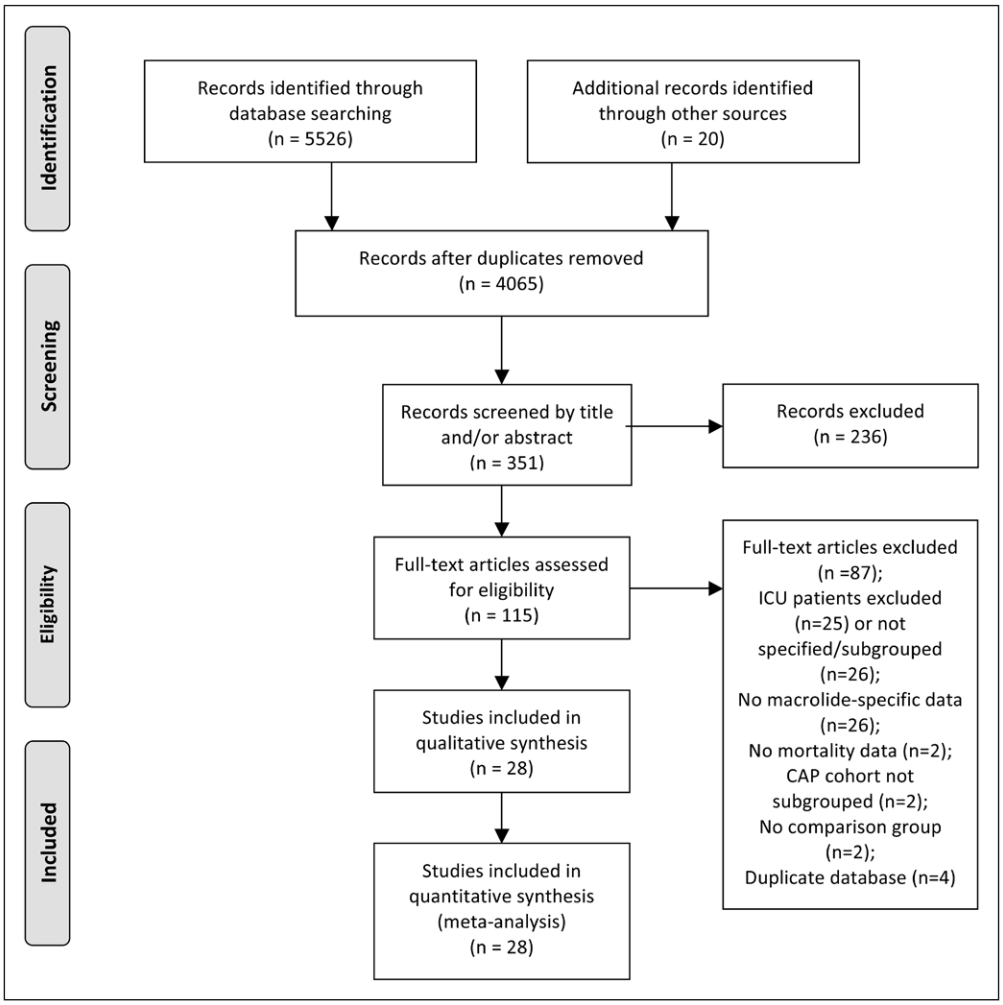

Figure 1. Flow diagram of study selection process. CAP = community-acquired pneumonia.

Study Characteristics

Twenty-eight full-text publications were included in our review, all of which were observational cohort studies (12–14, 25–49). Unpublished data were sought from 48 authors. Thirty authors (63%) responded, 18 of whom provided data (13, 25, 27–35, 37–41, 43, 50). In general, included studies tended to be smaller (average sample size, 336) but more often multicenter (17 of 28; 61%), and

most were retrospective (15 of 28; 54%). Other study characteristics can be found in **Table 1**.

Quality Assessment

Our quality assessment is shown in Table 1. On a 9-point scale, the median risk of bias score according to the Newcastle-Ottawa instrument was 8—all studies were considered high-quality nonrandomized observational studies. The interrater agreement (κ statistic) was 0.92. The main risks of biases were selection bias (e.g., in all studies given the lack of random allocation) and information bias (e.g., administrative database studies where clinical data were not available to confirm diagnoses).

Primary Analysis: Macrolide Treatment and Mortality

We identified 9,850 critically ill patients with CAP in 27 studies for our primary analysis (12–14, 25–48). The average age ranged from 58 to 78 years and 14–49% were women. Pneumonia Severity Index was the most commonly used measure of disease severity (67% of studies), 8–95% of patients presented with septic shock and 37–100% required mechanical ventilation (Table 1). Four thousand thirty-six patients (41%) received macrolide therapy. Overall short-term all-cause mortality was 22%, varying from a low of 10% (29) to a high of 50% (39) in included studies. Four studies reported multiple outcomes, for example, in-hospital and 30-day mortality (13, 26, 27, 47). For each of these studies, we chose to use 30-day mortality in our analyses. Macrolide use was associated with a statistically significant lower risk of mortality compared with nonmacrolide use (21% [846 of 4,036 patients] vs 24% [1,369 of 5,814]; RR, 0.82; 95% CI, 0.70–0.97; $p = 0.02$) (**Fig. 2**). Heterogeneity was substantial ($I^2 = 63\%$).

Subgroup Analyses

First, we excluded patients who received macrolide monotherapy and observed that macrolide combination therapy (25 studies, 8,872 patients) (12, 14, 25–35, 37–47, 50) was associated with a marginally significant lower mortality compared with nonmacrolide therapies (21% [737 of 3,447 patients] vs 23% [1,245 of 5,425]; RR, 0.84; 95% CI, 0.71–1.00; $p = 0.05$; $I^2 = 60\%$).

Second, among critically ill patients treated with BLM versus BLF therapy (19 studies, 4,241 patients) (12, 25–27, 29, 30, 32, 33, 35, 38–45, 47, 50), a trend ($p = 0.09$) to reduced mortality in the BLM (20% [511 of 2,561 patients]) versus BLF group (23% [386 of 1,680]; RR, 0.83; 95% CI, 0.67–1.03) was observed and heterogeneity reduced ($I^2 = 25\%$).

Third, when restricted to prospective studies (12 studies, 2,356 patients, or 25% of available data) (12, 14, 25, 27–30, 35, 36, 38, 39, 44), we did not observe a mortality difference between patients treated with macrolide and nonmacrolide therapies (24% [225 of 934 patients] vs 23% [334 of 1,422]; RR, 0.90; 95% CI, 0.73–1.11; $p = 0.32$; $I^2 = 35\%$).

Fourth, among those requiring mechanical ventilation (four studies, 718 patients) (12, 36, 43, 44), a trend ($p = 0.06$) toward a reduction in mortality with macrolide use compared with nonmacrolide therapies was observed (27% [61 of 229 patients] vs 32% [158 of 489]; RR, 0.79; 95% CI, 0.61–1.01; $p = 0.06$; $I^2 = 0\%$).

Fifth, in a small number of patients with septic shock (four studies, 484 patients) (14, 43, 44, 47), macrolide use was not associated with a statistically significant reduction in mortality compared with nonmacrolide therapies (36% [83 of 233 patients] vs 42% [105 of 251]; RR, 0.82; 95% CI, 0.49–1.37; $p = 0.45$; $I^2 = 56\%$), although there was an absolute 6% difference in mortality between groups.

Sixth, among critically ill patients with pneumococcal CAP (six studies, 499 patients), macrolide use was not associated with a mortality reduction compared with nonmacrolide therapies (32% [102 of 319 patients] vs 24% [43 of 180]; RR, 1.17; 95% CI, 0.76–1.78; $p = 0.48$; $I^2 = 35\%$).

Last, pooled adjusted risk estimates (nine estimates from eight studies; $n = 2{,}629$) (12, 26, 43–45, 47–49) indicated a statistically significant mortality benefit with macrolide use compared with nonmacrolide therapy that was larger than that seen in our primary analysis (adjusted RR, 0.75; 95% CI, 0.58–0.96; $p = 0.02$; $I^2 = 57\%$) (**Fig. 3**).

There was no evidence of publication bias (funnel plots were symmetric and Egger test $p > 0.05$ in all analyses).

DISCUSSION

In this systematic review and meta-analysis of almost 10,000 critically ill patients with CAP, we observed a statistically significant 18% relative decrease in crude mortality associated with the use of macrolides when compared with non–macrolide-containing antimicrobial regimens (3% absolute reduction; RR, 0.82; 95% CI, 0.70–0.97; $p = 0.02$). Although heterogeneity was present, the findings were robust to most of our a priori subgroup analyses. When we restricted only to patients who received macrolide combination therapy, a similar 16% relative risk reduction in mortality was observed and heterogeneity reduced. In addition, a similar 17% reduction in mortality was observed with BLM versus BLF combination therapies, again with a reduction in heterogeneity. This comparison is nearly ideal in that both regimens provide almost identical antimicrobial spectra of action and would generally be considered guideline-concordant (23). Most noteworthy, perhaps, is the significant 25% relative mortality reduction observed when adjusted risk estimates were pooled. Although we were unable to show a benefit when analyses were restricted to prospective studies or when patients required mechanical ventilation or presented with septic shock, these three subgroup analyses were limited by much smaller sample sizes and in fact all demonstrated point estimates similar to our main analysis.

The results presented here are similar to those reported in our recently published meta-analysis examining macrolide use in hospitalized, noncritically ill (ward) patients (16). However, in our analysis in ward patients, when we restricted our analyses to randomized trials or guideline-concordant therapies, we were no longer able to demonstrate a mortality benefit with

macrolide therapy—suggesting confounding might explain the benefit observed in our primary analysis. In this meta-analysis, however, we demonstrated significant mortality benefit in almost all subgroups examined as well as our adjusted analysis. Is it plausible to try and reconcile these two different sets of conclusions drawn from two very different patient populations? We believe so. We hypothesize the observed benefit may relate to more robust systemic inflammation in critically ill patients with CAP (and thus greater opportunity for anti-inflammatory therapies to work) combined with a much higher event rate (22% in the ICU analysis vs 6% in the hospital ward analysis).

If our findings are not a result of chance, bias, or confounding, the mortality differences observed might relate, as mentioned above, to the non-antimicrobial immune modulatory properties of macrolides, including alterations in pro- and anti-inflammatory cytokines (tumor necrosis factor [TNF-α], interleukin [IL]-1, IL-6, IL-8, and interferon-γ), and decreased neutrophil chemotaxis, adhesion, and/or oxidative metabolism (51). In addition, macrolides have been shown to inhibit biofilm formation and decrease mucus hypersecretion, leading to improved mucociliary clearance (51). In a study examining patterns of cytokine gene expression (52) greater proinflammatory (IL-10 and TNF-α) messenger RNA levels were observed in ICU patients with severe sepsis and septic shock when compared with noncritically ill bacteremic patients or healthy controls. Furthermore, in a recent study in critically ill patients with ventilator-associated pneumonia (53), treatment with clarithromycin restored the balance between pro- and anti-inflammatory mediators in patients with sepsis.

Despite its strengths, our work has several limitations, most of which are limitations related to the available studies. First, we did not identify any randomized trials for inclusion and therefore could only pool observational studies. In addition, detailed patient demographic information, specifics of comparator treatments, and adjusted risk estimates were not available for many studies. Second, few of the included articles provided etiologic (microbiologic) information on CAP. Third, measures of inflammatory biomarkers—and the ability to compare degrees of systemic inflammation across studies—were not available in most studies and certainly not appropriate for any form of synthesis. In addition, information

TABLE 1. Study Characteristics

Study	Location	Design	Dates of Enrollment	Sample Size	Age (Mean or Median[a])	Sex (% Female)
Arnold et al (48, 50)[c,d]	International Multicenter (Community-Acquired Pneumonia Organization database)	Retrospective observational	2001–2010	704	NR	NR
Aspa et al (25)[d]	Spain Multicenter	Prospective observational	1999–2000	125 (data on 120; 96%)	58	27
Bratzler et al (26)[d]	USA Multicenter (Medicare database)	Retrospective observational	1998–1999 and 2000–2001	2,950	78	NR
Capelastegui et al (27)[d]	Spain Single center	Prospective observational	2000–2004	50	62	NR
Charles et al (28)[d]	Australia Multicenter	Prospective observational	2004–2006	94	NR	NR
Cillóniz et al (29)[d]	Spain Single center	Prospective observational	2003–2010	362 (data on 347; 96%)	63	36

regarding concomitant potentially immune-modulating therapies, such as corticosteroids or statins, was not available. Fourth, we could not examine the types, doses, durations, or timing of macrolide therapy (or the comparator antibiotics). A previous study (54) suggested that the propensity to prescribe specific therapies differs markedly among patients with CAP in observational studies, resulting in confounding by indication. However, our pooled risk-adjusted analysis should correct for at least some known confounders. Last, we could not undertake an individual patient data meta-analysis and the available data precluded meta-regression.

So, what is the clinical relevance of our findings? A randomized trial might be considered prohibitive, as to demonstrate a 3% absolute mortality difference with a control group event rate of 24% and 80% power would require approximately 6,200 patients in total. Until such a trial is conducted, our analysis represents a synthesis of the best available evidence. Our analysis might also suggest that "enough" observational studies of this question have been conducted and that a moratorium on nonrandomized studies might be in order. Regardless, based on our results, we would suggest that macrolide therapy may be of benefit in critically ill patients with CAP and should be used in combination as per guidelines.

CONCLUSIONS

In this systematic review and meta-analysis of observational studies including almost 10,000 patients, we found that macrolide use in the treatment of critically ill patients with CAP was associated with a robust and statistically significant 18% relative (3% absolute) reduction in crude mortality compared with nonmacrolide regimens and an even larger relative risk reduction in adjusted analyses. In the absence of randomized trial data, we believe this meta-analysis supports the use of macrolides as first-line combination treatment in critically ill patients with severe CAP and reinforces current guidelines for this high-risk population.

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Disease Severity Score (Mean or Median[a])	Mechanical Ventilation (%)	Septic Shock[b] (%)	Cohort Specifics	Overall Mortality	Risk of Bias (Ottawa-Newcastle Score)	Macrolide Use and Types
NR	NR	NR		21% 28-d mortality	Low (8)	49% NR
PSI: 79%; class IV/V	NR	82[e]	*Streptococcus pneumoniae*	32% 30-d mortality	Low (7)	65% Azithromycin Clarithromycin Erythromycin
PSI: 122; 83% class IV/V	NR	22[e]	≥ 65 yr	18% 30-d mortality	Low (8)	25% NR
PSI: 110; 68% class IV/V	NR	NR		14% 30-d mortality	Low (7)	16% NR
NR	90[f]	45[e]		15% 30-d mortality	Low (7)	97% Azithromycin Roxithromycin Erythromycin
PSI: 73%; class IV/V	37	20	ICU only	10% in-hospital mortality	Low (7)	21% Azithromycin Clarithromycin

(*Continued*)

TABLE 1. (*Continued*). Study Characteristics

Study	Location	Design	Dates of Enrollment	Sample Size	Age (Mean or Median[a])	Sex (% Female)
Dambrava et al (30)[d]	Spain Single center	Prospective observational	2001–2004	71	67[a]	
Frei et al (42) (abstract only)	USA (TX) Multicenter	Retrospective observational	1999–2000	55	70	49
Grenier et al (31)[d]	Canada (QC) Single center	Retrospective observational	1997–2008	478	68	NR
Karhu et al (47)	Finland Single center	Retrospective observational	2000–2010	210	55[a]	35
Kontou et al (32)[d]	USA (CT) Single center	Retrospective observational	1999–2003	31	61	42
Le-Bris-Tomczak et al (33)[d]	France Single center	Retrospective observational	2006–2009	40	65[a]	35
Marras et al (34)[d]	Canada (ON) Multicenter	Retrospective observational	1997–2000	54	72	30
Martin-Loeches et al (12)	Europe Multicenter	Prospective observational	2007–2008	257	61	32
Menéndez et al (35)[d]	Spain Multicenter	Prospective observational	2005–2007	306	NR	NR
Minhas et al (41)[d]	Canada (ON) Single center	Retrospective observational	2002–2005	7 (data on 6; 86%)	66	14
Mongardon et al (46)	France Multicenter	Retrospective observational	2001–2008	222	60	34
Pascual et al (36)	USA (CA) Single center	Prospective observational	1994–1997	144	63	48

Disease Severity Score (Mean or Median[a])	Mechanical Ventilation (%)	Septic Shock[b] (%)	Cohort Specifics	Overall Mortality	Risk of Bias (Ottawa-Newcastle Score)	Macrolide Use and Types
PSI: 92%; class IV/V	58[f]	63[e]		14% 30-d mortality	Low (8)	56% NR
PSI: 120[a] beta-lactam/macrolide combination therapy, 130[a] beta-lactam/fluoroquinolone combination therapy	NR	NR	ICU only	14% in-hospital mortality	NA	29% NR
PSI: 110	NR	NR		19% 30-d mortality	Low (8)	22% Azithromycin Clarithromycin Erythromycin
Infectious Diseases Society of America/American Thoracic Society severe community-acquired pneumonia criteria 76%	52	43		20% 30-d mortality	Low (8)	Azithromycin Erythromycin
PSI: 81%; class IV/V	65	16	*S. pneumoniae*	32% in-hospital mortality	Low (8)	35% Azithromycin
NR	75	63	ICU only; *S. pneumoniae*	38% in-hospital mortality	Low (7)	75% NR
PSI: 135; 82% class IV/V	NR	NR		24% in-hospital mortality	Low (7)	43% Azithromycin Clarithromycin Erythromycin
SAPS II: 47, Sequential Organ Failure Assessment: 8	100	76[g]	ICU only; all MV	37% ICU mortality	Low (8)	21% Azithromycin Clarithromycin
NR	NR	NR		15% in-hospital mortality	Low (8)	26% NR
PSI: 143	NR	NR		33% in-hospital mortality	Low (7)	33% Azithromycin Clarithromycin
SAPS II: 47[a] Logistic Organ Dysfunction System: 8[a]	84	76	ICU only; *S. pneumoniae*	29% in-hospital mortality	Low (8)	73% NR
APACHE II: 21 SAPS: 13	100	48	ICU only; all MV	46% in-hospital mortality	Low (8)	47% Erythromycin

(*Continued*)

TABLE 1. (*Continued*). Study Characteristics

Study	Location	Design	Dates of Enrollment	Sample Size	Age (Mean or Median[a])	Sex (% Female)
Rello et al (37)	Spain Multicenter	Retrospective observational	1991–1992 and 1993–1999	460	59[a]	24
Restrepo et al (13)[d]	USA (TX) Multicenter	Retrospective observational	1999–2002	100	NR	NR
Rodrigo et al (49)	England and Wales Multicenter	Prospective observational	2009–2011	419	NR	NR
Rodríguez et al (14)	Spain Multicenter	Prospective observational	2000–2002	529	60	28
Rosón et al (38)[d]	Spain Single center	Prospective observational	1995–2000	101	59	NR
Shorr et al (43)[d]	USA (WA) Single center	Retrospective observational	2010	101	62	43
Sligl et al (44)	Canada (AB) Multicenter	Prospective observational	2000–2002	328	61	45
Song et al (39)[d]	Asia Multicenter	Prospective observational	2002–2004	48	NR	NR
Wilson and Ferguson (40)[d]	Australia Multicenter	Retrospective observational	2001–2003	96	60	44
Wilson et al (45)	USA Multicenter (Veterans Affairs database)	Retrospective observational	2001–2007	1989	74	1

NR = not reported, PSI = Pneumonia Severity Index, NA = not applicable, SAPS = Simplified Acute Physiology Score, MV = mechanical ventilation, APACHE = Acute Physiology and Chronic Health Evaluation.

[a]The numbers in the column are reported as means unless followed by an [a], in which case they are medians.

[b]Shock defined as systolic blood pressure < 90 mm Hg or vasopressor dependence.

[c]Duplicate database studies. 2013 data were used for our primary and adjusted analyses. Subgroup data had been previously obtained from 2009 data so these were used in our macrolide combination and beta-lactam/macrolide combination therapy versus beta-lactam/fluoroquinolone combination therapy subgroup analyses.

[d]Unpublished ICU subgroup data provided by authors (total of 18).

[e]Assuming all patients with shock were admitted to ICU.

[f]Assuming all patients requiring mechanical ventilation were admitted to ICU.

[g]Severe sepsis and septic shock combined cohort.

[h]Adjusted risk estimate reported for ICU cohort; crude data not reported.

[i]A clinical prediction rule for predicting mortality in community-acquired pneumonia including *c*onfusion of new onset, blood *u*rea nitrogen > 7 mmol/L (19 mg/dL) *r*espiratory rate ≥ 30 breaths per minute, *b*lood pressure < 90 mm Hg systolic or ≤ 60 mm Hg diastolic, age ≥ *65* yr.

Disease Severity Score (Mean or Median[a])	Mechanical Ventilation (%)	Septic Shock[b] (%)	Cohort Specifics	Overall Mortality	Risk of Bias (Ottawa-Newcastle Score)	Macrolide Use and Types
APACHE II: 20[a]	67	30	ICU only	30% ICU mortality	Low (7)	63% NR
NR	NR	NR	Severe sepsis	30% 30-d mortality	Low (8)	47% Azithromycin Clarithromycin Erythromycin
NR	36	NR	31	NR[h]	Low (8)	Azithromycin Clarithromycin Erythromycin
APACHE II: 19	66	51	ICU only	28% 28-d mortality	Low (8)	55% Clarithromycin Erythromycin
PSI: 129; 80% class IV/V	NR	NR		35% 30-d mortality	Low (8)	55% Clarithromycin Erythromycin
CURB-65[i]: 3.5	81	95		25% in-hospital mortality	NA	51% Azithromycin
PSI: 116; 73% class IV/V; APACHE II: 17	84	8	ICU only	16% 30-d mortality	Low (8)	28% Azithromycin Clarithromycin Erythromycin
NR	NR	NR		50% 30-d mortality	Low (8)	31% NR
PSI: 113; 72% class IV/V	73	63	ICU only	33% in-hospital mortality	Low (7)	73% NR
NR	39	24	ICU only; ≥ 65 yr	25% 30-d mortality	Low (8)	56% Azithromycin Clarithromycin Erythromycin

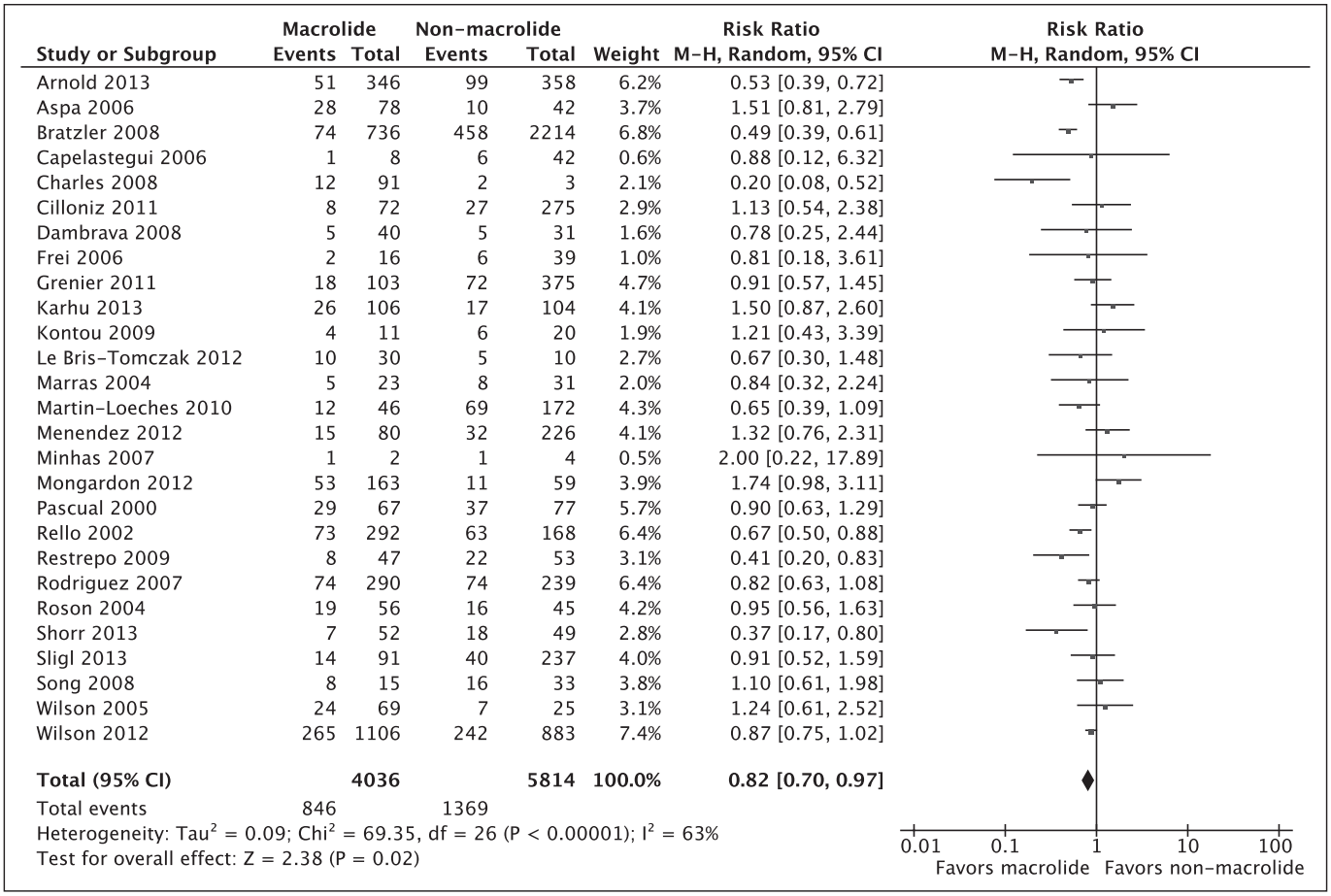

Figure 2. Macrolide versus nonmacrolide therapy and mortality in critically ill patients with community-acquired pneumonia: primary analysis ($n = 27$). M-H = Mantel-Haenszel.

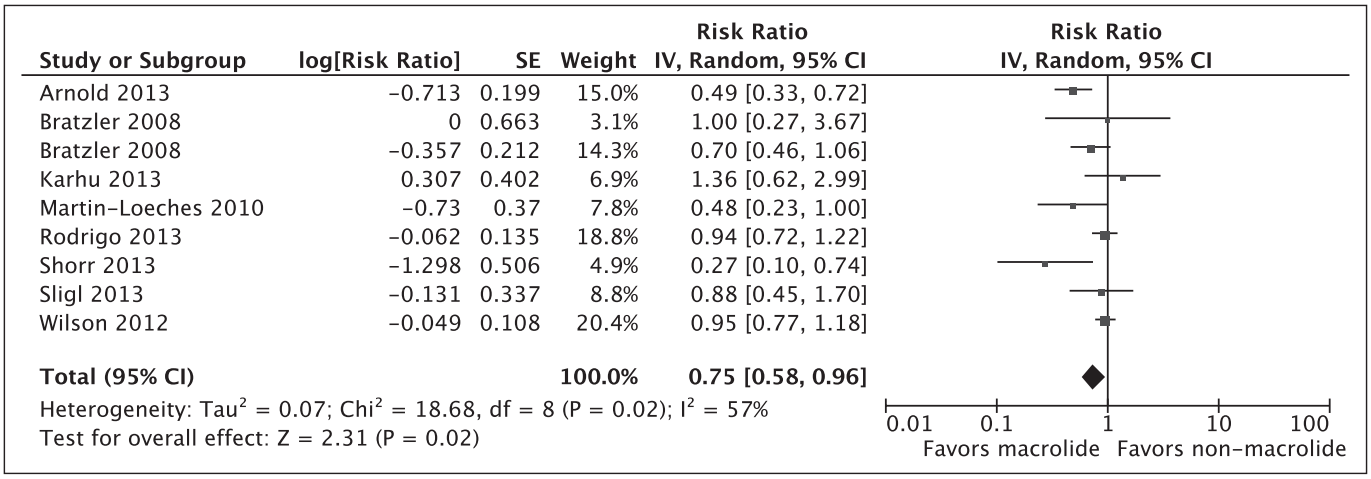

Figure 3. Macrolide versus nonmacrolide therapy and mortality in critically ill patients with community-acquired pneumonia: pooled adjusted risk estimates ($n = 9$).

(30); Grenier et al (31); Kontou et al (32); Le-Bris-Tomczak et al (33); Marras et al (34); Menéndez et al (35); Minhas et al (41); Restrepo et al (13); Rosón et al (38); Shorr et al (43); Song et al (39); and Wilson and Ferguson (40). All those who have contributed significantly to this work have been acknowledged.

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