Treatment of Mycoplasma Pneumonia: A Systematic Review

BACKGROUND AND OBJECTIVE: Children with community-acquired lower respiratory tract infection (CA-LRTI) commonly receive antibiotics for Mycoplasma pneumoniae. The objective was to evaluate the effect of treating M. pneumoniae in children with CA-LRTI.

METHODS: PubMed, Cochrane Central Register of Controlled Trials, and bibliography review. A search was conducted by using Medical Subject Headings terms related to CA-LRTI and M. pneumoniae and was not restricted by language. Eligible studies included randomized controlled trials (RCTs) and observational studies of children ≤17 years old with confirmed M. pneumoniae and a diagnosis of CA-LRTI; each must have also compared treatment regimens with and without spectrum of activity against M. pneumoniae. Data extraction and quality assessment were completed independently by multiple reviewers before arriving at a consensus. Data were pooled using a random effects model.

RESULTS: Sixteen articles detailing 17 studies were included. The most commonly selected primary outcome was symptomatic improvement. Nine studies examined M. pneumoniae treatment in CA-LRTI secondary to M. pneumoniae, and 5 RCTs met criteria for meta-analysis. The suggested pooled risk difference of 0.12 (95% confidence interval, 0.04 to 0.20) favoring treatment was not significantly different and demonstrated significant heterogeneity. Limitations included substantial bias and subjective outcomes within the individual studies, difficulty interpreting testing modalities, and the inability to correct for mixed infections or timing of intervention.

CONCLUSIONS: We identified insufficient evidence to support or refute treatment of M. pneumoniae in CA-LRTI. These data highlight the need for well-designed, prospective RCTs assessing the effect of treating M. pneumoniae in CA-LRTI.

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KEYWORDS
pediatric, pneumonia, macrolide, azithromycin, atypical pneumonia, mycoplasma

ABBREVIATIONS
CA-LRTI—community-acquired lower respiratory tract infection
CAP—community-acquired pneumonia
CI—95% confidence interval
IDSA—Infectious Diseases Society of America
RCT—randomized controlled trial
URTI—upper respiratory tract infection

Dr Biondi conceptualized and designed the review, reviewed articles, ran the meta-analysis, and drafted the original manuscript; Dr McCulloh conceptualized and designed the review, reviewed articles, helped to run the meta-analysis, and drafted the original manuscript; Dr Alverson participated in the design, helped interpret the included studies, and critically reviewed the manuscript; Mr Klein participated in study design, tabulated articles, and reviewed the manuscript; Ms Dixon participated in study design, helped perform the literature review, and critically reviewed portions of the manuscript; Dr Ralston participated in study design, supervised Drs Biondi and McCulloh in study interpretation and translated 1 study, and participated in the meta-analysis; and all authors approved the final manuscript as submitted.

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Community-acquired pneumonia (CAP) accounts for >150,000 pediatric hospitalizations each year in the United States, and there are great disparities in patterns of care and outcomes. Specifically, wide variations in antibiotic prescribing practices exist among physicians, often because the causative agent is not identified. For this reason, recent evidence-based pediatric CAP practice guidelines published by the Infectious Diseases Society of America (IDSA) recommend that children hospitalized with CAP be tested for Mycoplasma pneumoniae. Mycoplasma pneumoniae is a common cause of CAP and other community-acquired lower respiratory tract infections (CA-LRTIs), particularly in school-age children and adolescents, but there are large gaps in our understanding of this disease. Prevalence estimates vary from 10% to 40% in pediatric CA-LRTI, and few studies address treatment recommendations. Additionally, the IDSA guidelines target the use of macrolides in CA-LRTI as an area needing additional research.

First-line treatment of children hospitalized with CAP currently includes a β-lactam to treat common causative bacterial agents such as Streptococcus pneumoniae and a macrolide to provide additionally treatment of atypical pathogens such as M. pneumoniae. Studies of antibiotic use in the pre-IDS guidelines era showed marked variability in prescription practices, probably because the efficacy of macrolides in the treatment of M. pneumoniae remains unclear and treatment recommendations, even in major textbooks, are variable. The available evidence is also conflicting. One small trial suggests that β-lactam use in children with CAP is more cost-effective than macrolides, several randomized controlled trials (RCTs) suggest no difference in efficacy, and 2 recent pediatric cohort studies suggest that β-lactam–macrolide combination therapy decreased length of stay by 20% to 30% over β-lactam monotherapy. Data on antibiotic treatment of pediatric CA-LRTI caused by M. pneumoniae are generally considered inconclusive, but macrolides remain the most commonly overprescribed antibiotic at pediatric clinics in the United States: >6 million annual doses for respiratory symptoms without a clear indication.

A Cochrane review on the use of antibiotics to treat CA-LRTI secondary to M. pneumoniae in children found insufficient evidence to draw any specific conclusions about the efficacy of antibiotics for the condition. However, this review omitted at least 3 RCTs (roughly one-third of the total RCTs) for which there appeared to be applicable data on the topic, and data from observational studies were omitted. The objective of our study was to provide a more comprehensive review of all available published literature on the use of antibiotics in children to treat CA-LRTI secondary to M. pneumoniae.

**METHODS**

**Search Design**

This was a systematic review of all observational and randomized trials comparing antibiotics with spectrum of activity for M. pneumoniae (eg, macrolide, tetracycline, or quinolone class) with placebo or antibiotics from any other class without spectrum of activity against M. pneumoniae in children <18 years of age with CA-LRTI. The review was conducted in concordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.

**Outcome Types**

The primary outcome was clinical improvement or cure at follow-up. Clinical improvement or cure could include resolution of fever; resolution or improvement in symptoms such as cough, congestion, shortness of breath, fatigue, or chest pain; or improvement or cure as defined by the authors of the individual studies.

**Literature Search**

With the assistance of a librarian (A.D.), we performed a comprehensive search of PubMed (January 1966–August 2012) with the Medical Subject Headings terms and keywords (Table 1). After duplicates were removed, we used inclusion and exclusion criteria to select studies based on their title and abstract to include in our review. Additional studies were identified through manual search of the bibliographies of qualifying studies. Before manuscript submission, a second search was performed (August 2012–September 2013) to ensure that the review was as up-to-date as possible and any new studies were included in the analysis.

**Study Selection**

Studies were considered eligible for inclusion in the review if they met the

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**TABLE 1** Medical Subject Headings Used for Primary Literature Search

<table>
<thead>
<tr>
<th>Mycoplasma pneumoniae</th>
<th>antibiotic*</th>
</tr>
</thead>
<tbody>
<tr>
<td>pneumonia, mycoplasma</td>
<td>anti-bacterial agents</td>
</tr>
<tr>
<td>respiratory tract infections</td>
<td>macrolide*</td>
</tr>
<tr>
<td>pneumonia</td>
<td>roxithromycin</td>
</tr>
<tr>
<td>recurrent respiratory tract infection*</td>
<td>erythromycin</td>
</tr>
<tr>
<td>respiratory infection*</td>
<td>telithromycin</td>
</tr>
<tr>
<td>RRTI</td>
<td>macrolides</td>
</tr>
<tr>
<td>community-acquired infections</td>
<td>azithromycin</td>
</tr>
<tr>
<td>lower respiratory tract infection*</td>
<td>clarithromycin</td>
</tr>
<tr>
<td>lower respiratory infection*</td>
<td>pediatric*</td>
</tr>
<tr>
<td>infant</td>
<td>child</td>
</tr>
<tr>
<td>child, preschool</td>
<td>adolescent</td>
</tr>
</tbody>
</table>

* Represents open-ended term.
following criteria: randomized or observational studies, included children ≤17 years of age, included ≥10 children who were diagnosed with CA-LRTI secondary to laboratory-confirmed M. pneumoniae, data were provided for at least 1 outcome measuring improvement, and the study compared any antibiotic with spectrum of activity against M. pneumoniae with either placebo or another antibiotic without activity against M. pneumoniae. Studies that examined children with chronic respiratory illnesses such as cystic fibrosis, bronchiectasis, bronchopulmonary dysplasia, congenital heart disease, or immunodeficiency were excluded, as were those that examined children with nosocomial and congenital infections.

Studies were considered eligible for meta-analysis if, in addition to meeting criteria for inclusion in the qualitative review, information was either provided or could be extrapolated regarding the total number and outcomes of patients with M. pneumoniae within each treatment group. A subgroup analysis of the initial meta-analysis was performed that included only the RCTs.

Identification of Trials and Data Extraction

The principal investigators (E.B. and R.M.) independently screened each citation identified through the initial search strategy as definitely, possibly, or clearly not meeting inclusion criteria. Full-text articles of all studies definitely or possibly meeting inclusion criteria were obtained regardless of primary language of the publication. Reviewers (E.B. and R.M.) independently reviewed each full-text article and then reached consensus before data abstraction. For full-text articles meeting study criteria, reviewers (E.B. and R.M.) extracted data for each study independently and then discussed their findings to form a consensus. Discrepancies were resolved through discussion with the collaborating reviewers (B.A. and S.R.). When necessary, the principal reviewers attempted to contact study authors to verify methods and extracted data, although no responses were received.

Validity and Quality Assessment

Studies were assessed and graded for level of evidence based on criteria published by the Oxford Center for Evidence-Based Medicine. An 18-item study quality assessment tool (Supplemental Information) was developed based on recommendations published by the Agency for Healthcare Research and Quality. Items on the quality assessment tool fell within 6 domains: subject selection, study performance bias, detection bias, subject attrition, reporting bias, and financial conflict of interest. Items were marked as factor present, not present, or unclear based on review of the manuscript. Each study was given a total quality score, and for this purpose, labels of “not present” or “unclear” were grouped together. Studies were considered to be unblinded when it was not specifically stated that participants or investigators were blinded. Three reviewers (E.B., R.M., and B.A.) performed individual assessments on all included studies independently and then discussed each until all 3 reviewers were in agreement.

Statistical Analyses

Because much of the information relevant to this review was extrapolated from data presented in the included studies, the review authors attempted to calculate statistical significance wherever possible using $\chi^2$ or Fisher’s exact tests. In cases for which M. pneumoniae and Chlamydia pneumoniae were grouped together, a “worst-case scenario” was performed by the review authors that assumed all C. pneumoniae were in the “improved on treatment” group. These were then subtracted from the total. This allowed an interpretation of the results that would ensure that, if a treatment effect was identified, it was not secondary to C. pneumoniae. For comparison, the analysis was also performed assuming that C. pneumoniae and M. pneumoniae responded equally to treatment. Treatment effects for dichotomous outcomes were calculated as risk difference using random effects modeling. Study heterogeneity was assumed for a $P < .10$ and I² ≥25%. If the primary outcome (clinical improvement) was assessed in separate methods and separate time periods, each set of outcomes was included in the review and meta-analysis. Meta-analysis was performed by using Comprehensive Meta-Analysis Version 2 (Biostat, Englewood, NJ).

RESULTS

The initial database search identified 4867 articles. One other citation was identified via bibliography review. Most articles were excluded based on a preliminary screen of the abstracts, leaving 40 full-text articles to be assessed for eligibility. Before submission, a second search was performed (August 2012–September 2013) to ensure that no recent articles were missed in the review. This search revealed 275 new articles, 1 of which was assessed for full-text eligibility but did not meet study criteria. Of the 4943 total citations reviewed, 16 met criteria for inclusion in the qualitative synthesis. One RCT used different outcome metrics at 2 different times and, for the purposes of this review, was considered 2 separate RCTs. Therefore, 17 studies were included. Four citations were non-English and were translated by the review authors (2 in Spanish, 1 in French, and 1 in German). Eight studies provided
data or enabled the review authors (E.B. and R.M.) to extract specifically comparing treatment with no treatment of M. pneumoniae in children diagnosed with M. pneumoniae and were included in the quantitative analysis; 5 were RCTs (Fig 1).

There were 4294 patients enrolled in the 17 included studies (Table 2). Of these, an aggregate 2648 patients could be used to compare an agent treating M. pneumoniae with an agent that did not treat M. pneumoniae in CA-LRTI. This number excludes comparator arms in which antibiotics of the same class or spectrum were compared and patients in whom therapy could not be determined. One randomized trial provided data on a total of 155 patients but compared macrolide treatment with either a β-lactam or another macrolide and did not provide separate statistics.

Ten RCTs and 3 cohort studies compared a macrolide with a nonmacrolide in the treatment of CA-LRTI. One RCT compared levofloxacin with a β-lactam, 1 retrospective cohort study compared M. pneumoniae spectrum with non-M. pneumoniae spectrum antibiotics, and 2 case–control studies compared macrolide treatment in patients with macrolide-sensitive and macrolide-resistant M. pneumoniae. Esposito et al included upper respiratory infections (URTs) (199/352, 57%) in addition to CA-LRTI (153/352, 43%) but did not provide a separate analysis, and therefore all are included in this review, as was done previously. One study did not report the total number of pediatric patients. Studies used various combinations of methods for M. pneumoniae detection; 5 used culture of nasopharyngeal specimens, and 6 used polymerase chain reaction assays of upper airway specimens. No trials were placebo controlled, and a number of studies received pharmaceutical company funding.

When we evaluated for overall quality among all studies included, detection bias, which included items such as validity and reliability of study outcomes, was the most frequently identified bias category (12/17 studies, 71%) (Table 3). The most common cause of study performance bias was unblinded participants or observers. More than half of the RCTs (6/11, 55%) reported a potential conflict of interest, which in all cases was pharmaceutical sponsorship with use of that company’s drug in the study.

**Spectrum-Specific Treatment in Pediatric CA-LRTI Secondary to M. pneumoniae**

Nine studies provided enough detail to allow a comparison of M. pneumoniae spectrum and non-spectrum treatment in pediatric patients with CA-LRTI secondary to M. pneumoniae and included a total of 723 such patients (Table 4). In terms of overall clinical improvement, 4 of 5 RCTs found no clinical benefit. One retrospective cohort study identified a significant improvement in duration of fever in patients treated with macrolides, although clinically there was a large overlap in fever duration range (3.0–6.8 vs 3.4–7.9 days; \( P = .04 \)), and there was not a significant

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**FIGURE 1**

Flowchart for included studies. *One article used 2 different outcome metrics at 2 different time periods and was therefore treated as 2 separate studies.*
### TABLE 2  Study Characteristics and Quality, in Chronological Order

<table>
<thead>
<tr>
<th>Study</th>
<th>Design/Length</th>
<th>Patients</th>
<th>Intervention/Comparator</th>
<th>Relevant Outcomes</th>
<th>Relevant Results</th>
<th>Level of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterner et al (1967)</td>
<td>RCT/1.5 y</td>
<td>N = 180 (unknown ages) with CAP</td>
<td>EES/cephaloridine</td>
<td>failure = daily fevers for 5 d or fever ≥10 d</td>
<td>8/87 (EES) vs 17/83 (cephaloridine) failures. Mean fever = 2.7 vs 3.8 d. In those with MP, 0/13 vs 3/9 failures. Does not separate adults and children.</td>
<td>2b</td>
</tr>
<tr>
<td>Ruhrmann et al (1982)</td>
<td>RCT/1 y</td>
<td>N = 120 (6 mo–14 yr) with CAP</td>
<td>EES/amoxicillin</td>
<td>Fever duration</td>
<td>Mean fever = 2.6 ± 4.1 d (EES) vs 2.4 ± 1.9 d (amoxicillin).</td>
<td>2b</td>
</tr>
<tr>
<td>Garo et al (1988)</td>
<td>Retro, multisite cohort/5 y</td>
<td>N = 182 (mean age = 29 y) with MP</td>
<td>MP spectrum/no spectrum</td>
<td>Fever duration</td>
<td>Mean fever = 3 d (spectrum) vs 7 d (no spectrum). 84% presented with atypical pneumonia. Does not separate adults and children.</td>
<td>4</td>
</tr>
<tr>
<td>Gomez Campdera et al (1996)</td>
<td>RCT/2 y</td>
<td>N = 155 (6 mo–16 y) with CAP</td>
<td>AZM/co-amoxiclav (&lt;5 y); EES (≥5 y)</td>
<td>Cured or improved at 3, 10, or 30 d</td>
<td>At 3, 10, and 30 d, respectively: 78/82 (AZM) vs 66/73 (comparator); 80/82 vs 69/73 (AZM); 80/82 vs 69/73. No difference in duration of fever or cough. 15 total with MP.</td>
<td>2b</td>
</tr>
<tr>
<td>Harris et al (1998)</td>
<td>Multisite, RCT/1.5 y</td>
<td>N = 456 (6 mo–16 y) with CAP</td>
<td>AZM/co-amoxiclav (&lt;5 yr); EES (≥5 yr)</td>
<td>1. Cured or improved at 15–19 d 2. Cured or improved at 4–6 wk 3. Adverse events</td>
<td>Success in 50/55 (AZM) vs 46/53 (co-amoxiclav) at 1–13 d and 439/503 vs 145/170 at 10–17 d.</td>
<td>1b</td>
</tr>
<tr>
<td>Sáez-Llorens et al (1998)</td>
<td>Multisite, RCT/2 y</td>
<td>N = 335 (6 mo–15 y) with CAP</td>
<td>AZM/co-amoxiclav (&lt;5 y); EES (≥5 yr)</td>
<td>Cured or improved after 3 d of treatment</td>
<td>96/97 (AZM) vs 114/116 (co-amoxiclav) cured or improved. In cases of MP, 9/9 and 5/5 cured or improved.</td>
<td>2b</td>
</tr>
<tr>
<td>Wubbel et al (1999)</td>
<td>RCT/2 y</td>
<td>N = 174 (6 mo–16 y) with CAP</td>
<td>AZM/co-amoxiclav (&lt;5 y); EES (≥5 yr)</td>
<td>1. Cured 3 d after treatment 2. Adverse events</td>
<td>Success in 50/55 (AZM) vs 46/53 (co-amoxiclav) at 10–13 d and 46/51 vs 43/50 at 25–30 d. 33/59 vs 41/58 adverse events.</td>
<td>2b</td>
</tr>
<tr>
<td>Ferwerda et al (2001)</td>
<td>Multisite, RCT/3 y</td>
<td>N = 118 (3 mo–12 y) with CAP</td>
<td>AZM-co-amoxiclav</td>
<td>1. Cured or improved at 10–13 d 2. Cured or improved at 25–30 d 3. Adverse events</td>
<td>Success in 50/55 (AZM) vs 46/53 (co-amoxiclav) at 10–13 d and 46/51 vs 43/50 at 25–30 d. 33/59 vs 41/58 adverse events.</td>
<td>1b</td>
</tr>
<tr>
<td>Principi et al (2001)</td>
<td>Pro, multisite cohort/1 y</td>
<td>N = 615 (2–14 y) with CAP</td>
<td>Macrolide/no spectrum</td>
<td>Cured or improved at 4–6 wk</td>
<td>Mean fever = 1.7 d (AZM) vs 2.0 d (amoxicillin). By day 14 all 47 CXRs had improved by &gt;75%.</td>
<td>2b</td>
</tr>
<tr>
<td>Kogan et al (2003)</td>
<td>RCT/3 y</td>
<td>N = 110 (30 d–14 y) with CAP</td>
<td>Classic CAP; AZM/amoxicillin</td>
<td>Clinical response: Fever duration CXR &gt;75% improved</td>
<td>Clinical success at 4–6 wk 76/76 (AZM) vs 88/114 (comparator) with MP or CP had clinical success (P &lt; .001).</td>
<td>2b</td>
</tr>
<tr>
<td>Esposito et al (2005), study A</td>
<td>RCT/2 y</td>
<td>N = 352 (1–14 y) with recurrent RTI</td>
<td>AZM and symptomatic/ symptomatic</td>
<td>Clinical success at 4–6 wk</td>
<td>Success was 409/441 (levoflaxacin) vs 138/147 (comparator) at 1–3 d and 439/503 vs 145/170 at 10–17 d.</td>
<td>2b</td>
</tr>
<tr>
<td>Esposito et al (2005), study B</td>
<td>RCT/2 y</td>
<td>N = 352 (1–14 y) with recurrent RTI</td>
<td>AZM and symptomatic/ symptomatic</td>
<td>≤2 RTIs at 6 mo</td>
<td>Success was 409/441 (levoflaxacin) vs 138/147 (comparator) at 1–3 d and 439/503 vs 145/170 at 10–17 d.</td>
<td>2b</td>
</tr>
<tr>
<td>Bradley et al (2007)</td>
<td>Multisite, RCT/2 y</td>
<td>N = 738 (6 mo–16 y) with CAP</td>
<td>Levoflaxacin/β-lactam (&lt;5 y); macrolide (≥5 y)</td>
<td>Improved or cured at 1–3 d and cured at 10–17 d</td>
<td>Mean fever = 4.90 ± 1.89 d (macrolide) vs 5.63 ± 2.22 d (no macrolide) (P = .04).</td>
<td>2b</td>
</tr>
<tr>
<td>Lu et al (2008)</td>
<td>Retro, cohort/2 y</td>
<td>N = 139 (8 mo–12 y) with MP CA-RTI</td>
<td>Macrolide/no macrolide</td>
<td>Duration of fever</td>
<td>Mean fever = 4.90 ± 1.89 d (macrolide) vs 5.63 ± 2.22 d (no macrolide) (P = .04).</td>
<td>2b</td>
</tr>
<tr>
<td>Matsubara et al (2009)</td>
<td>Retro, case–control/4 y</td>
<td>N = 94 (0–14 y) with MP CAP treated with macrolide</td>
<td>Macrolide sensitive MP/ resistant MP</td>
<td>1. Excellent or good clinical response 2. Mean fever duration 3. Cough duration</td>
<td>43/47 (sensitive) vs 5/22 (resistant) had positive clinical response (P &lt; .01). Mean fever = 1.5 vs 4.0 d (P &lt; .01) and mean cough = 1.5 vs 4.0 d (P &lt; .01).</td>
<td>3b</td>
</tr>
</tbody>
</table>
difference in other signs or symptoms, white blood cell count, or C-reactive protein levels. One retrospective case–control study found an overall clinical benefit and 2 other studies identified a decrease in fever duration, although these were rated as being among the lowest quality of evidence in this review. Esposito et al (study A) was the only RCT to identify a clinical benefit, but the patient population included children with URTI. Additionally, the data were categorized only as “atypical” bacteria and did not separate C. pneumoniae from M. pneumoniae. Twenty-seven patients had acute C. pneumoniae infection only, and the “worst-case scenario” excludes all patients with C. pneumoniae after assuming each improved on macrolide therapy.

Two meta-analyses were attempted using risk difference as the treatment effect. The first included all studies listed in Table 4 that used dichotomous variables. However, there was a large degree of heterogeneity (P < .001) in addition to publication bias and largely variable treatment effects. A second analysis used only the RCTs and demonstrated a pooled risk difference of 0.12 (95% confidence interval [CI], −0.04 to 0.20) (Fig 2). This risk difference represents the absolute change in risk attributable to treatment with a macrolide. In our case, the risk in the treated group minus the risk in the control group was 12% (95% CI, −4% to 20%). This finding suggests that 12% of children treated with a macrolide will have more rapid clinical improvement, corresponding to a number needed to treat of 8.33, but the confidence interval overlapping 0% negates statistical significance. There remained significant heterogeneity between the studies (P = .02). The funnel plot revealed potential for publication bias against small studies that show a treatment effect (Fig 3). To provide comparison with the “worst-case scenario,” the same meta-analysis, assuming C. pneumoniae and M. pneumoniae responded equally to treatment, demonstrated a pooled risk difference of 0.12 (95% CI, 0.01 to 0.22).

**DISCUSSION**

The majority of studies included in our systematic review did not show a significant clinical benefit of M. pneumoniae spectrum therapy in CA-LRTI. Of the 9 studies that specifically examined the issue of M. pneumoniae treatment in children with CA-LRTI secondary to M. pneumoniae, almost all the prospective studies showed no clinical benefit. The remaining studies generally suggest a statistical, but not necessarily clinically relevant, decrease in fever duration, and most of these are rated as low- or lowest-quality evidence. Our meta-analysis of RCTs suggests a small treatment benefit in patients with CA-LRTI secondary to M. pneumoniae. However, the pooled effect favoring treatment was driven primarily by the result of a single RCT that included children with URTIs (57% of enrolled patients). Four of the 5 studies included in the meta-analysis did not show a benefit of M. pneumoniae spectrum therapy, and the summary statistic is not statistically significant. The associated funnel plot demonstrates a paucity of small studies showing a treatment effect, suggesting either publication bias against such studies, poor methodological design, or artifact heterogeneity among smaller studies.

The question of M. pneumoniae spectrum (specifically macrolide) use in CAP, or other CA-LRTIs, is commonly encountered in pediatric practice. Two large, retrospective cohort studies based on administrative data sets have indirectly addressed the issue of M. pneumoniae treatment by comparing differences in length of hospital stay among children receiving β-lactam
monotherapy and children receiving combination therapy with a macrolide.\textsuperscript{2,31} These studies found a shorter length of stay among children receiving combination therapy. However, testing for \textit{M. pneumoniae} was not recorded in either database and therefore could not be assessed. Macrolides are among the most frequently prescribed classes of antibiotics for respiratory tract infections in children, particularly in conditions for which antibiotics are not clearly indicated.\textsuperscript{15} Additionally, national guidelines intended to reduce practice variability in the management of CAP in children recommend consideration of macrolide use but state that this is based on limited data.\textsuperscript{3} Our review found insufficient evidence to support or refute antibiotic use in CA-LRTI secondary to \textit{M. pneumoniae}. This suggests that macrolide use in CA-LRTI could represent an area of opportunity for reducing antibiotic use, which could have a significant impact on health care costs and the development of antimicrobial resistance.\textsuperscript{32,33}

Our review provides novel information in comparison with the previous review on the topic by including more enrolled patients (4294 vs 1912) and more studies (17 vs 7).\textsuperscript{10} Although the previous review reports insufficient data to draw conclusions, we suggest that the available literature does not currently support treatment of CA-LRTI secondary to \textit{M. pneumoniae}. We examined observational studies, many of which were assessed as having the same level of evidence as the RCTs. In the absence of high-quality RCTs, experts suggest it is reasonable to include cohort and case–control studies in a systematic review, particularly when the quality of evidence is equivocal.\textsuperscript{34} Additionally, we identified 3 randomized trials that had not been previously examined, 1 of which was assessed as having the highest level of evidence of any included study.\textsuperscript{12,16,17}

Although our review failed to identify clear therapeutic efficacy of macrolides in pediatric CA-LRTI due to \textit{M. pneumoniae}, there are data in support of antibiotic treatment. Military studies from the 1960s, performed on recruits in

### TABLE 3 Bias Assessment for Individual Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection</th>
<th>Performance</th>
<th>Detection</th>
<th>Attrition</th>
<th>Reporting</th>
<th>Conflict of Interest</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sterner et al (1967)</td>
<td>x</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>4/15</td>
</tr>
<tr>
<td>Garo et al (1983)</td>
<td>x</td>
<td>x</td>
<td>—</td>
<td>—</td>
<td>x</td>
<td>—</td>
<td>8/14</td>
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<tr>
<td>Gomez Campdera et al (1996)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>7/17</td>
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<tr>
<td>Gendrel et al (1997)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>8/14</td>
</tr>
<tr>
<td>Harris et al (1998)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>x</td>
<td>—</td>
<td>x</td>
<td>4/15</td>
</tr>
<tr>
<td>Wubbel et al (1999)</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>x</td>
<td>—</td>
<td>3/15</td>
</tr>
</tbody>
</table>

\(\ldots\), substantial bias not identified within the domain; x, substantial bias identified within the domain.

### TABLE 4 Studies Comparing Spectrum With Nonspectrum Treatment of Children With Acute Respiratory Infection With \textit{M. pneumoniae} Grouped by Outcome Term\textsuperscript{a}

<table>
<thead>
<tr>
<th>Study</th>
<th>Time Frame</th>
<th>Outcome</th>
<th>Treatment (n)</th>
<th>Comparator (n)</th>
<th>(P^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Improved</td>
<td>Improved</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>Total</td>
<td></td>
</tr>
</tbody>
</table>

\(\ldots\), substantial bias not identified within the domain; x, substantial bias identified within the domain.

\(a\) Numbers often extrapolated by the review authors.

\(b\) Includes \(P\) values calculated by the review authors.

\(c\) Results are mean ± SD.

\(d\) Worst-case scenario with all 27 \textit{C. pneumoniae} patients placed in the treatment improved group and then excluded.
basic training, found that recruits
with atypical pneumonia more often
had serologic evidence of
*M. pneumoniae*
infection (identified as Eaton’s agent
at the time) than asymptomatic con-
trols.35,36 Additionally, in a random-
ized, double-blind, placebo-controlled
study among 300 recruits with atypi-
cal pneumonia due to *M. pneumoniae*,
treatment with a tetracycline was found
to decrease the duration of a number of
clinical signs and symptoms faster than
placebo.37 These seminal studies do not
necessarily represent the typical cli-
nical situation encountered by pedia-
tricians today, given their young adult,
homogenous population, nor can they
account for mixed infections or mod-
ernized diagnostic testing. Nonetheless,
these studies describe principles of
study design and conduct in this area
that can serve as a template for pedi-
atric investigations.

One of the strengths of meta-analysis is
in the process of evaluating the avail-
able literature for heterogeneity. It is
often difficult to find a middle ground
between throwing out all summary
estimates and inappropriately com-
bining studies, particularly in pediat-
rics, where the paucity of high-quality
RCTs is acute. We provided a summary
statistic for 1 broad study question, but
we noted significant study heteroge-
neity that we could not resolve with
subgroup analysis. Therefore, our in-
terpretation of the entirety of the sta-
tistical testing associated with our
meta-analysis is that despite multiple

<table>
<thead>
<tr>
<th>Study name</th>
<th>Risk Difference (95% CI)</th>
<th>Weight (%)</th>
<th>Risk Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bradley et al.</td>
<td>0.06 (-0.13 – 0.25)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Esposito et al. (A)</td>
<td>0.23 (0.15 – 0.31)</td>
<td>28</td>
<td></td>
</tr>
<tr>
<td>Esposito et al. (B)</td>
<td>0.02 (-0.15 – 0.19)</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Harris et al.</td>
<td>0.00 (-0.15 – 0.15)</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Sáez-Llorens et al.</td>
<td>0.00 (-0.26 – 0.26)</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Overall effect</td>
<td>0.12 (-0.04 – 0.20)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

$I^2 = 65.4, p = 0.02$

**FIGURE 2**
Meta-analysis of randomized trials comparing spectrum and nonspectrum treatment of *M. pneumoniae* in children. Studies were weighted by size and degree
of heterogeneity. The overall effect (diamond) represents the pooled risk differences of the 5 studies. The confidence interval crosses 0.00, suggesting a lack
of statistical significance.

**FIGURE 3**
Funnel plot of standard errors by risk difference for all studies in the second meta-analysis. Publication bias is evident against small studies that show
a treatment effect.
studies, a clear treatment effect has not emerged. Furthermore, the study heterogeneity lends credence to the idea that a large RCT is necessary to provide guidance to pediatricians on this clinical question.

There are several limitations to our review, most related to the quality of the available data on the topic. First, most studies contained substantial bias or financial conflict of interest. We attempted to account for this through in-depth quality assessment and reporting to allow a critical interpretation of study results. In particular, detection bias was commonly identified in the studies comparing spectrum with nonspectrum therapy in patients diagnosed with *M. pneumoniae*. This bias most often represented lack of blinding of investigators or participants or lack of a reliable outcome measure (ie, clinical improvement). This quality issue could potentially skew study results toward or away from the null hypothesis.

Second, we were unable to extract data on outcomes for all studies, reducing the number of articles that could be included in the meta-analysis and potentially causing publication bias. This limitation should be balanced against the fact that we abstracted quantitative data from more studies than previous meta-analyses on this subject.

Third, our assessment of treatment effect was limited primarily to subjective outcome measures such as symptomatic improvement or resolution. This limitation is inevitable given the primary endpoints used in the included studies, but our bias assessment specifically addresses the subjective nature of the data.

Fourth, *M. pneumoniae* testing modalities have changed dramatically over time, with variable testing characteristics and lack of overall consistency. This limits the uniformity of the patient population included in our review. Furthermore, coinfection with a pathogen in addition to *M. pneumoniae* is common but rarely identified via clinical testing, making it difficult to draw specific conclusions about therapeutic effects.5,38

Finally, no study included in our analysis took into account the duration of illness before the start of antibiotic therapy. It is possible that the timing of intervention relative to the start of symptoms is related to the outcome.

**CONCLUSIONS**

Our systematic review provides insufficient evidence to support conclusions about the efficacy of macrolide treatment of CA-LRTI due to *M. pneumoniae* in children. Fever duration may be decreased, but the clinical impact of this effect is unclear, and we identified few high-quality studies to support it. Our review represents the most comprehensive evaluation of treating *M. pneumoniae* in children with CA-LRTI to date. The findings from this review highlight the need for high-quality, prospective studies to assess the impact of antibiotic therapy to treat CA-LRTI caused by *M. pneumoniae* in children. These studies should specifically address the potential for confounding mixed infections, timing of intervention relative to symptom onset, and testing modalities that include a combination of serology and polymerase chain reaction assays.

**ACKNOWLEDGMENTS**

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*Pediatrics*; originally published online May 26, 2014;
DOI: 10.1542/peds.2013-3729

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