Empirical Atypical Coverage for Inpatients With Community-Acquired Pneumonia

Systematic Review of Randomized Controlled Trials

Daphna Shefet, MD; Eyal Robenshtok, MD; Mical Paul, MD; Leonard Leibovici, MD

Background: Current guidelines of empirical antibiotic treatment for inpatients with community-acquired pneumonia recommend antibiotics whose spectrum covers intracellular (atypical) pathogens. No sufficient evidence exists to support the necessity of such coverage, whereas limiting it may reduce toxic effects, resistance, and expense. Our goal was to assess the efficacy of empirical coverage of atypical pathogens in terms of mortality and clinical and bacteriological success.

Methods: Systematic review and meta-analysis of randomized, controlled trials comparing treatment regimens with and without coverage of atypical pathogens. We searched MEDLINE, EMBASE, the Cochrane Library, and references. Relative risks (RRs) with 95% confidence intervals (CIs) were pooled using the fixed-effects model. The primary outcome assessed was all-cause mortality.

Results: We included 24 trials encompassing 5015 patients. We found no studies of a drug without atypical coverage that compared it with the same drug supplemented with a drug with atypical coverage; nearly all compared a β-lactam with a single quinolone or macrolide. There was no difference in mortality between the 2 arms (RR, 1.13 [95% CI, 0.82-1.54]). Regimens with coverage of atypical pathogens showed a trend toward clinical success and a significant advantage to bacteriological eradication. Both disappeared when evaluating methodologically high-quality studies alone. These regimens further showed a significant advantage in clinical success for *Legionella pneumophila*, whereas no advantage for pneumococcal pneumonia was seen. There was no difference between study arms in the frequency of total adverse events.

Conclusion: Empirical antibiotic coverage of atypical pathogens in hospitalized patients with community-acquired pneumonia showed no benefit of survival or clinical efficacy in this synthesis of randomized trials.


MAJOR GUIDELINES for the treatment of community-acquired pneumonia (CAP) generally differentiate between outpatients, inpatients, and patients hospitalized in intensive care units.\(^1\)\(^4\) Suggested antibiotic regimens for inpatients include a β-lactam combined with macrolides, or monotherapy with a respiratory fluoroquinolone. Although *Streptococcus pneumoniae* remains the leading pathogen in CAP, the rationale for a macrolide supplement or fluoroquinolone monotherapy lies in its ability to cover intracellular (atypical) pathogens such as *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Legionella pneumophila*.

Coverage of the latter pathogen is recommended explicitly for patients in intensive care units. To our knowledge, no randomized, controlled trial has compared, as an objective, the superiority of antibiotic regimens containing coverage of atypical pathogens with regimens lacking such coverage. A systematic review of nonrandomized studies found a significant reduction in mortality when the antibiotic spectrum covered atypical pathogens in 6 of its 8 selected studies.\(^3\) However, all studies were cohort studies, and 2 were restricted to bacteremic pneumococcal pneumonia.\(^6\)\(^7\) In the largest study,\(^8\) the choice of such regimens was associated with an initial lower severity score, thus underlining the potential bias of nonrandomized studies. Whereas the advantage of combination therapy is unproved, dual therapy may increase toxic effects, resistance, and cost. Moreover, an antagonism between penicillin and erythromycin has been shown in vitro and in...
vivo against *S pneumoniae* isolates, the most prevalent pathogen causing CAP.10,11

The present review evaluates the need for empirical antibiotic coverage of atypical pathogens in adults hospitalized owing to CAP. It includes all randomized, controlled trials that compared an antibiotic regimen containing coverage of atypical pathogens with one not containing such coverage. The main outcome was mortality. Secondary outcomes included clinical efficacy, bacteriological failure, and adverse events.

### METHODS

#### INCLUSION CRITERIA

We included randomized, controlled trials that assessed treatment of CAP in hospitalized adults and in which an antibiotic regimen containing coverage of atypical pathogens was compared with a regimen not containing such coverage. Regimens including a macrolide, fluoroquinolone, tetracycline, doxycycline, or chloramphenicol were considered to afford atypical coverage. Regimens lacking these drugs were considered regimens without atypical coverage. We included oral and intravenous therapies.

Trials that included mainly patients with major immunosuppressive states were not considered for this review. Trials with a dropout rate of more than 30% were excluded.

#### SEARCH STRATEGY

The search string combined community-acquired infections/pneumonia, inpatients, and antibiotic names and classes of atypical drugs identified in the previous section (string specified at *The Cochrane Database of Systematic Reviews* 2003, Issue 2). Databases searched included CENTRAL (Cochrane Library Issue 4, 2004), MEDLINE (to August 2004), and EMBASE (to July 2003). We inspected references of identified studies for more trials and contacted corresponding authors for complementary information.

#### OUTCOMES

The primary outcome was overall mortality up to 30 days after the end of treatment. Secondary outcomes included clinical treatment failure, bacteriological eradication, and development of superinfections and adverse events, specifically gastrointestinal events or events resulting in treatment discontinuation.

#### DATA EXTRACTION

Outcomes were extracted by intention to treat (ITT), including all individuals randomized in the outcome assessment. When data for ITT analysis were unavailable, available cases were assessed. Two reviewers (D.S. and E.R.) independently extracted data from included trials. Methodological assessment was performed using a component approach, including allocation generation and concealment, blinding, and analysis by ITT. Allocation generation and concealment were classified as adequate, unclear, or inadequate, using criteria from the *Cochrane Reviewers’ Handbook* 4.2.2.12 We did not assess a composite quality scale, because different scales may lead to discordant results.13 Sensitivity analyses were performed to assess the robustness of the findings per the following trial methods: allocation concealment, allocation generation, and blinding.

#### RESULTS

### DESCRIPTION OF STUDIES

Our search resulted in 994 references. Fifty-six publications were retrieved for full-text inspection, of which 26 fulfilled the inclusion criteria. Two were withdrawn from analysis owing to unavailable data, and thus 24 trials are included in the review (Table 1 and Figure 1).

### DATA ANALYSIS

Relative risks (RRs) with 95% confidence intervals (CIs) are reported. We used a fixed-effects model when significant heterogeneity between trials was observed. Heterogeneity of trial results was assessed by calculating a *χ*² test of heterogeneity and the *I*² measure of inconsistency. Significant heterogeneity was predefined as a *χ*² test *P* value smaller than .1 or an *I*² measure larger than 50%. We had anticipated between-trial variation in the estimation of morbidity and mortality for different geographic areas, age groups, sample size, and the drug affording atypical coverage (macrolides or fluoroquinolones). Subgroup analyses to assess the impact of these factors on the main results were performed. A funnel plot estimating the trial precision (logarithm of the RR for efficacy against sample size) was examined to estimate potential asymmetry.
Included studies were performed between 1982 and 2004 and encompassed 5015 patients. Inclusion criteria in all studies consisted of adults hospitalized with CAP. The number of participants was 100 or fewer in 8 trials and more than 100 in 16 trials (range, 40-808 participants). All trials were restricted to adults, with a mean age less than 65 years in 12 studies and 65 years or greater in 9. Among the latter, 2 studies were performed in nursing homes,54,62 and 1 exclusively included patients older than 70 years.65 Three studies did not report mean age. Ten studies provided the percentage of patients with chronic obstructive pulmonary disease, ranging from 25% to 52.5%.64 None analyzed separately results for patients with chronic obstructive pulmonary disease and/or smokers.

Pneumonia was defined by a combination of clinical signs, radiological confirmation (the sole criteria in 2 studies).54,62 Some participants received 400 mg/d while others received 200 mg/d (both optional in the study design). For the methodology of the studies, see the full meta-analysis as published in The Cochrane Database of Systematic Reviews 2005, Issue 2.

Table 1. Included Studies

<table>
<thead>
<tr>
<th>Source</th>
<th>Country</th>
<th>Treatment (No. of Randomized Patients)†</th>
<th>Mean Age, y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aubier et al,46 1998</td>
<td>MC Europe</td>
<td>Oral sparfloxacin, 400 mg/d (159) Oral azithromycin, 500 mg/d (36)</td>
<td>42</td>
</tr>
<tr>
<td>Bothe et al,47 1995</td>
<td>MC Europe</td>
<td>Oral azithromycin, 500 mg/d (36)</td>
<td>53</td>
</tr>
<tr>
<td>Carbon et al,48 1992</td>
<td>MC France</td>
<td>Oral temafloxacin, 600 mg BID (125) Oral ofloxacin, 200 mg BID (several, 400 mg BID) (59)</td>
<td>55</td>
</tr>
<tr>
<td>Chuard and Regamey,49 1989</td>
<td>MC Germany</td>
<td>Oral ofloxacin, 200 mg BID (several, 375 mg QID) (62)</td>
<td>66</td>
</tr>
<tr>
<td>Feldman et al,50,51 2001</td>
<td>MC worldwide</td>
<td>Intravenous sitafloxacin, 400 mg/d (35) Intravenous combined imipenem and cilastatin, 500 mg TID (34)</td>
<td>43</td>
</tr>
<tr>
<td>Fourrier et al,52 1986</td>
<td>France</td>
<td>Oral pefloxacin, 1200 mg/d (20) Customary treatment of β-lactam, cephalosporin, and antistaphylococcal (20)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Genne et al,53 1997</td>
<td>Switzerland</td>
<td>Intravenous clarithromycin, 500 mg BID 3-5 days, followed by oral clarithromycin, 500 mg BID (56)</td>
<td>70</td>
</tr>
<tr>
<td>Gleadhill et al,54 1986</td>
<td>United States</td>
<td>Oral ciprofloxacin, 500 mg BID (26) Intravenous ciprofloxacin, 2 g/d, followed by intramuscular ceftriaxone, 1 g/d (26)</td>
<td>71</td>
</tr>
<tr>
<td>Hirata-Dulas et al,55 1991</td>
<td>United States</td>
<td>Intravenous ciprofloxacin, 200-400 mg BID, followed by oral ciprofloxacin, 750 mg BID (24)</td>
<td>79</td>
</tr>
<tr>
<td>Kalbermatter et al,56 2000</td>
<td>Argentina</td>
<td>Oral levofloxacin, 500 mg BID (28) Intravenous amoxicillin-clavulanate, 1 g TID (28)</td>
<td>60</td>
</tr>
<tr>
<td>Khan and Basir,57 1989</td>
<td>United States</td>
<td>Intravenous ciprofloxacin, 200 mg BID (74) Intravenous ceftazidime, 2 g BID-TID (71)</td>
<td>58</td>
</tr>
<tr>
<td>Kobayashi et al,58 1984</td>
<td>Japan</td>
<td>Oral levofloxacin, 200 mg TID (42) Oral amoxicillin, 1 g BID, and clavulanate, 125 mg TID (156)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Lephonte et al,59 2004</td>
<td>MC worldwide</td>
<td>Oral gemifloxacin, 320 mg/d (168)</td>
<td>54</td>
</tr>
<tr>
<td>Lode et al,60 1995</td>
<td>MC Europe</td>
<td>Oral sparfloxacin, 200 mg/d (401), oral erythromycin, 1g BID (208) Oral amoxicillin, 500 mg TID, and clavulanic acid, 125 mg TID (199)</td>
<td>54</td>
</tr>
<tr>
<td>Miki et al,61 1994</td>
<td>Japan</td>
<td>Intravenous levofloxacin, 500 mg BID, followed by oral levofloxacin, 500 mg BID (319)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Miki et al,62 1998</td>
<td>Japan</td>
<td>Intravenous levofloxacin, 500 mg BID, followed by oral levofloxacin, 500 mg BID (319)</td>
<td>65</td>
</tr>
<tr>
<td>Norrby et al,63 1998</td>
<td>MC worldwide</td>
<td>Intravenous ceftriaxone, 4 g/d (306) Intravenous ceftriaxone, 1 g BID (28)</td>
<td>58</td>
</tr>
<tr>
<td>Peterson et al,64 1988</td>
<td>United States</td>
<td>Intravenous ciprofloxacin, 750 mg BID (30) Intravenous meropenem, 500 mg TID (52)</td>
<td>76</td>
</tr>
<tr>
<td>Petitpretz et al,65 2001</td>
<td>MC worldwide</td>
<td>Intravenous moxifloxacin, 400 mg/d (203) Intravenous imipenem-cilastatin, 500 mg TID (51)</td>
<td></td>
</tr>
</tbody>
</table>
ies), laboratory values, and/or bacteriological evidence. Thirteen trials further included outpatients, patients with nosocomial pneumonia, and/or patients with bronchi- 
s. In all cases, most of the patients had CAP or could undergo separate analysis.

The antibiotic regimens, dosages, and routes of ad-
ministration are detailed in Table 1. In nearly all studies,
the comparison was between monotherapy in the arm covering atypical pathogens and a β-lactam. We found no comparison of a β-lactam–macrolide combination with β-lactam monotherapy. Treatment duration was con-
voyed in 14 studies and was almost uniformly 10 days, 
with no difference between the arms. The main out-
come in all studies was clinical treatment failure. Six stud-
ies mandated radiological resolution for success defini-
tion, and 1 required bacteriological eradication. None 
chose mortality as the primary outcome.

Eighteen trials assessed bacteriological failure (per pa-
tient or per pathogen). Only 8 performed serologic tests 
for atypical pathogens, of which 1 study found negative re-
sults for all tests, and 4 others did not fully report eradica-
tion rates. Superinfection and colonization rates were re-
ported in only 5 studies each, precluding further evaluation.

Adverse events were addressed in all studies, although 
2 did not specify the number of events per treatment arm.

METHODOLOGICAL QUALITY 
OF INCLUDED STUDIES

Of the 24 included studies, adequate allocation conceal-
ment was reported in 6 and adequate allocation genera-
tion in 9. No information was available for the remain-
ing studies. All studies of adequate allocation concealment 
were also of adequate allocation generation.

Seven studies reported results by ITT. Another 13 re-
ported the number of dropouts per study arm, permit-
ting reanalysis by ITT by assuming failure for all drop-
outs. Four studies did not refer to dropouts and were 
analyzed only by patients undergoing evaluation.

Follow-up duration was specified in 21 studies, of 
which 16 defined a specific time for outcome measure-
ment. Follow-up ranged from the end of treatment to 3 
months after. Overall mortality was assessed at the end 
of treatment or at follow-up in all studies. Data at the far-
thest point in time, up to 30 days, was chosen for analy-
sis. At least 18 of the 24 studies were sponsored by phar-
maceutical companies, all of which manufactured the drug 
with atypical coverage.

OVERALL MORTALITY

Twenty-three of the 24 studies could be evaluated for 
mortality, encompassing 4846 of 5015 randomized 
patients (96.6%) (Figure 2). Six studies reported no 
deaths, whereas 10 reported mortality rates of 0.4% to 
5%; 6, 5% to 8%, and 1, 25%. There was no signifi-
cant difference between the arms in the overall mortality rate 
(RR, 1.13 [95% CI, 0.82-1.54]) (Figure 2). The differ-
ence was nonsignificant when evaluating quinolones 
(RR, 0.98; 95% CI, 0.69-1.41) and macrolides (RR, 1.25 
[95% CI, 0.52-3.01]). No heterogeneity was seen for the 
overall comparison.

Mortality was further analyzed by age, geographic 
area, and sample size, and the results disclosed no sig-
nificant difference. Overall mortality in both arms was 
similar when analyzing studies per allocation genera-
tion, allocation concealment, blinding, and the ITT 
analysis (Table 2). In the funnel plot for overall mor-
tality, results are symmetrically centered around the 
combined RR.

CLINICAL FAILURE

Clinical failure was the primary outcome in all studies, 
comprising 4682 patients. No significant difference be-
tween study arms was observed (RR, 0.92 [95% CI, 0.82-
1.03]) (Figure 3).

When we evaluated the different drug regimens, op-
posing trends were visible, with an advantage for quinolone monotherapy (RR, 0.89 [95% CI, 0.77-1.02]) 
and a disadvantage for macrolide monotherapy (RR, 1.17 
[95% CI, 0.77-1.77]). Clinical failure with macrolide 
treatment was the only comparison in which heterogene-
ity was detected (χ²=6.68; P=.08; I²=55.1%). Reanalysis 
by the random-effects model did not alter the results. 
Relative risks were similar regardless of age or sample 
size. An advantage for coverage of atypical pathogens 
was statistically significant in the 13 European studies 
(RR, 0.82 [95% CI, 0.70-0.95]), but not in studies per-
formed elsewhere.

When we analyzed studies by methodological qual-
ity, an advantage toward coverage of atypical pathogens 
was accentuated in studies of unclear or inadequate 
allocation concealment and allocation generation. In 
the analysis of studies of high methodological quality, 
the effect was nearly identical in the 2 arms (for 
aequate allocation generation, RR, 0.99 [95% CI, 0.82-
1.19]; for adequate allocation concealment, RR, 0.98 
[95% CI, 0.81-1.19]) (Table 2). In an ITT vs per-
protocol design sensitivity analysis, no significant dif-
fERENCE was found.

Clinical treatment failure rates were evaluated among 
patients with microbiologically documented infections. 
No significant difference between the study arms in the 
treatment of documented pneumococcal infections was 
detected (RR, 1.15 [95% CI, 0.81-1.63] among 16 studies 
and 906 patients). Data were insufficient to analyze 
cases of pneumococcal bacteremia. For atypical patho-
gens, a trend in favor of atypical coverage did not reach 
statistical significance (RR, 0.52 [95% CI, 0.24-1.10] 
among 4 studies and 158 patients). A significant advan-
tage to coverage of atypical pathogens was found for eradica-
tion of Legionella species, with an RR of 0.17 and nar-
row 95% CIs (0.05-0.63), based on relatively few cases 
(n=43). Sixty-one of 78 atypical cases and 9 of 20 cases of 
L pneumophila were successfully resolved in the arm 
without coverage of atypical pathogens.

BACTERIOLOGICAL ERADICATION

Eighteen studies reported bacteriological eradication rates, 
comprising 1995 patients and/or isolates. There was a 
statistically significant advantage to bacteriological eradi-
cation for the arm covering atypical pathogens (RR, 0.73
Figure 2. The number of patients who died within the follow-up period (overall mortality). The left side depicts arms with atypical coverage; the right side, arms without atypical coverage. A value of less than 1 favors atypical coverage. Studies are subdivided by the antibiotic used as the atypical regimen, including quinolone therapy (01), macrolide therapy (02), and combined macrolide and quinolone therapy (03). The total indicates the total number of patients (sum of groups 01-03). CAP indicates community-acquired pneumonia; CI, confidence interval; I², measure of inconsistency (see “Methods” section); n/N, number of patients/total number of patients in the study; RR, relative risk; and solid oblong diamond, total events.
[95% CI, 0.59-0.91]), with no heterogeneity seen. However, in an analysis restricted to studies of adequate allocation generation and concealment, this advantage disappeared (RR, 0.96 [95% CI, 0.61-1.52]) (Table 2).

**ADVERSE EVENTS**

Adverse events per treatment arm were reported for 4261 patients. Total adverse events (RR, 1.02 [95% CI, 0.91-1.13]) and events requiring treatment discontinuation (RR, 0.98 [95% CI, 0.67-1.42]) were similar in both treatment arms, with no heterogeneity seen. Gastrointestinal events were reported in 15 studies and were significantly more common in the arm without atypical coverage (which consisted mainly of β-lactams) (RR, 0.73 [95% CI, 0.54-0.99]). However, the definitions of gastrointestinal events differed, some including abdominal pain and some diarrhea alone, thereby precluding an accurate comparison of antibiotic-associated diarrhea.

**COMMENT**

The objective of our review was to assess empirical antibiotic coverage of atypical pathogens in hospitalized patients with CAP, in terms of mortality and successful treatment. We found no difference in mortality between regimens with coverage of atypical pathogens and regimens without such coverage, persisting in all subgroup analyses. There was a nonsignificant trend toward clinical success of atypical pathogens, accentuated with quinolone monotherapy. The advantage disappeared when we evaluated high-quality methodological studies alone. A significant advantage in bacteriological eradication was detected in the coverage of atypical pathogens, especially in reference to *Legionella* species. This advantage was not demonstrated in an analysis restricted to studies of adequate allocation generation and concealment. There was no difference in the frequency of total adverse events between the 2 groups, although more gastrointestinal events (but not explicitly diarrhea) were noted in the arm without atypical coverage.

Mortality data were obtained for 96.6% of randomized patients. The overall mortality rate (adjusted mean mortality rate, 3.7%) was lower than that reported in the literature (eg, MedisGroups, 10.6%70; validation cohort inpatient mortality for the Pneumonia Patient Outcome Research Team, 8.0%71). This is surprising because nearly half of the studies target relatively severe pneumonia cases. Thus, patients recruited to randomized trials may not adequately represent all patients hospitalized with CAP.

Although mortality is the most significant outcome in a potentially lethal infection, all studies chose clinical failure as their primary outcome. This end point is subjective and should be studied with care. Our review clearly demonstrates its potential for bias. A trend in favor of clinical success for the arm covering atypical pathogens originated in studies with unclear allocation generation. Similarly, the clear statistical advantage of that arm, found in the overall analysis of bacteriological eradication rates, did not exist in an analysis restricted to studies of adequate allocation generation. Thus, we should be wary about relying solely on subjective outcomes when comparing treatment regimens for pneumonia, especially because pharmaceutical companies sponsored most studies and many studies were nonblinded.

The similar response of the young and old is somewhat surprising, as an advantage to atypical coverage would be expected in younger people with a higher prevalence of atypical pneumonia. Perhaps this prevalence diminishes in the hospitalized population. The clear advantage of the arm with atypical pathogen coverage in the successful treatment of *L pneumophila* infections is not surprising, although cases of atypical pneumonia (including *L pneumophila*) often resolved without such coverage. Coinfections with typical pathogens may explain some of these cases.

We had set out to investigate the contribution of coverage of atypical pathogens to empirical treatment of CAP in hospitalized patients. The most suitable study for our purpose would have been one comparing a drug without atypical coverage (eg, β-lactam) with a combination of that drug and a drug with atypical coverage (eg, β-lactam and a macrolide). None was found, although the need to add a macrolide to β-lactam therapy is a common dilemma manifested within the guidelines themselves. Furthermore, many studies included treatment arms that do not adhere to current guidelines. Therefore, our meta-analysis is chiefly based on comparison of various regimens without coverage of atypical pathogens to monotherapy, mainly quinolone monotherapy. Regarding this comparison, we found no advantage to coverage of atypical pathogens in terms of mortality or clinical success.

**Table 2. Sensitivity Analyses for Individual Methodological Quality Components**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adequate</th>
<th>Unclear or Inadequate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>1.06 (0.66-1.69)</td>
<td>1.18 (0.77-1.80)</td>
</tr>
<tr>
<td>No. of studies/patients</td>
<td>6/1390</td>
<td>17/3456</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>0.98 (0.81-1.19)</td>
<td>0.89 (0.77-1.02)</td>
</tr>
<tr>
<td>No. of studies/patients</td>
<td>6/1390</td>
<td>18/3292</td>
</tr>
<tr>
<td>Bacteriological failure</td>
<td>0.96 (0.61-1.52)</td>
<td>0.68 (0.53-0.86)</td>
</tr>
<tr>
<td>No. of studies/patients</td>
<td>5/469</td>
<td>13/1499</td>
</tr>
<tr>
<td>Allocation generation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall mortality</td>
<td>1.09 (0.69-1.73)</td>
<td>1.16 (0.76-1.77)</td>
</tr>
<tr>
<td>No. of studies/patients</td>
<td>9/1753</td>
<td>14/3093</td>
</tr>
<tr>
<td>Clinical failure</td>
<td>0.99 (0.82-1.19)</td>
<td>0.87 (0.77-1.01)</td>
</tr>
<tr>
<td>No. of studies/patients</td>
<td>9/1685</td>
<td>15/2997</td>
</tr>
<tr>
<td>Bacteriological failure</td>
<td>0.89 (0.60-1.30)</td>
<td>0.67 (0.52-0.87)</td>
</tr>
<tr>
<td>No. of studies/patients</td>
<td>7/602</td>
<td>11/1366</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; RR, relative risk.

*Combined effect estimates for each comparison are shown for studies reporting adequate vs unclear or inadequate methodological quality criteria.
### Figure 3.
The number of patients considered to have a clinical treatment failure. The left side depicts arms with atypical coverage; the right side, arms without atypical coverage. Studies are subdivided by the antibiotic used as the atypical regimen, including quinolone therapy (01), macrolide therapy (02), and combined macrolide and quinolone therapy (03). Total indicates the total number of patients (sum of groups 01-03). CAP indicate community-acquired pneumonia; CI, confidence interval; I², measure of inconsistency (see “Methods” section); n/N, number of patients/total number of patients in the study; RR, relative risk; and solid oblong diamond, total events.

<table>
<thead>
<tr>
<th>Study or Subcategory</th>
<th>Atypical Coverage, n/N</th>
<th>Nonatypical Coverage, n/N</th>
<th>Fixed RR (95% CI)</th>
<th>Weight, %</th>
<th>Fixed RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>01 Quinolone (Atypical Arm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Kobayashi et al,1984</td>
<td>4/41</td>
<td>0/33</td>
<td>0.11</td>
<td>7.29 (0.41-130.64)</td>
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<tr>
<td>Kalbermatter et al,2000</td>
<td>1/28</td>
<td>4/56</td>
<td>0.55</td>
<td>0.50 (0.06-4.27)</td>
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<td>Feldman et al,2001</td>
<td>3/35</td>
<td>3/34</td>
<td>0.89</td>
<td>0.37-2.14</td>
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<td>Vogel and Lode,1991</td>
<td>2/38</td>
<td>3/37</td>
<td>0.97</td>
<td>0.21-4.48</td>
<td></td>
</tr>
<tr>
<td>Gleasdale et al,1996</td>
<td>5/26</td>
<td>4/22</td>
<td>0.63</td>
<td>0.65 (0.11-3.67)</td>
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<td>Chuard and Regamey,1989</td>
<td>5/59</td>
<td>6/62</td>
<td>0.90</td>
<td>1.06 (0.32-3.46)</td>
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<tr>
<td>Khan and Basir,1989</td>
<td>6/66</td>
<td>6/56</td>
<td>1.22</td>
<td>0.88 (0.28-2.72)</td>
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</tr>
<tr>
<td>Fournier et al,1986</td>
<td>6/20</td>
<td>7/20</td>
<td>1.35</td>
<td>0.85 (0.29-2.48)</td>
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<td>Miki et al,1984</td>
<td>11/71</td>
<td>7/68</td>
<td>2.65</td>
<td>1.51 (0.62-3.66)</td>
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<tr>
<td>Peterson et al,1988</td>
<td>7/30</td>
<td>9/30</td>
<td>1.45</td>
<td>0.86 (0.35-2.10)</td>
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<td>Hirata-Dulas et al,1991</td>
<td>12/24</td>
<td>12/26</td>
<td>1.48</td>
<td>1.51 (0.62-3.66)</td>
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<td>Vandenbroucke,1990</td>
<td>21/75</td>
<td>21/81</td>
<td>2.39</td>
<td>1.08 (0.61-1.93)</td>
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<td>Aubier et al,1998</td>
<td>14/126</td>
<td>22/140</td>
<td>4.19</td>
<td>1.08 (0.64-1.81)</td>
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<td>Carbon et al,1992</td>
<td>19/123</td>
<td>24/120</td>
<td>4.33</td>
<td>0.71 (0.38-1.32)</td>
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<td>Tremolieres et al,1998</td>
<td>13/138</td>
<td>28/147</td>
<td>5.05</td>
<td>0.77 (0.45-1.33)</td>
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<tr>
<td>Rizzato et al,1997</td>
<td>7/110</td>
<td>28/115</td>
<td>5.69</td>
<td>0.26 (0.12-0.57)</td>
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<tr>
<td>Lephonte et al,2004</td>
<td>38/167</td>
<td>32/153</td>
<td>13.29</td>
<td>0.89 (0.75-1.17)</td>
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<tr>
<td>Petitprez et al,2001</td>
<td>46/200</td>
<td>44/208</td>
<td>71.78</td>
<td>0.89 (0.77-1.02)</td>
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<tr>
<td>Norby et al,1998</td>
<td>85/314</td>
<td>85/305</td>
<td>71.78</td>
<td>0.89 (0.77-1.02)</td>
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<tr>
<td>Subtotal</td>
<td>1691</td>
<td>1713</td>
<td>17.91</td>
<td>0.97 (0.75-1.25)</td>
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<tr>
<td>Total Events:</td>
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</tr>
<tr>
<td>305 (Atypical Coverage), 345 (Nonatypical)</td>
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<tr>
<td>Test for Heterogeneity: $\chi^2=21.13$ ($P=0.27$), I² = 14.8%</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>02 Macrolide (Atypical Arm)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zeluff et al,1988</td>
<td>3/46</td>
<td>0/44</td>
<td>0.11</td>
<td>6.70 (0.38-126.13)</td>
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<tr>
<td>Genne et al,1997</td>
<td>8/56</td>
<td>9/56</td>
<td>0.97</td>
<td>0.37-2.14</td>
<td></td>
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<tr>
<td>Bohle et al,1995</td>
<td>6/35</td>
<td>10/29</td>
<td>1.87</td>
<td>0.89 (0.37-2.14)</td>
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<tr>
<td>Romanelli et al,2002</td>
<td>23/101</td>
<td>14/103</td>
<td>2.27</td>
<td>0.50 (0.21-2.10)</td>
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<tr>
<td>Subtotal</td>
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<td>232</td>
<td>2.88</td>
<td>1.68 (0.91-3.07)</td>
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<tr>
<td>Total Events:</td>
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<td><strong>03 Combined Quinolone and Macrolide (Atypical Arm)</strong></td>
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<tr>
<td>Lode et al,1995</td>
<td>197/609</td>
<td>69/199</td>
<td>21.60</td>
<td>0.93 (0.75-1.71)</td>
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<tr>
<td>Subtotal</td>
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<td>21.60</td>
<td>0.93 (0.75-1.71)</td>
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<tr>
<td>Total Events:</td>
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<td></td>
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<tr>
<td>197 (Atypical Coverage), 69 (Nonatypical)</td>
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<tr>
<td>Test for Heterogeneity: Not Applicable</td>
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<tr>
<td>Test for Overall Effect: $Z=0.61$ ($P=0.54$)</td>
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<tr>
<td><strong>Total</strong></td>
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<tr>
<td>542 (Atypical Coverage), 447 (Nonatypical)</td>
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<tr>
<td>Test for Heterogeneity: $\chi^2=28.43$ ($P=0.02$), I² = 19.1%</td>
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</tbody>
</table>

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Our conclusion of no benefit might be due to lack of power when using available randomized trials. Large observational studies showed benefit for atypical coverage. However, correction for the baseline differences between patients given or not given atypical coverage in these studies may be impossible.

Studies designed specifically to evaluate the necessity of atypical coverage are needed. The optimal design would be a randomized controlled trial comparing the same β-lactam in both study arms with and without the addition of antibiotics against atypical pathogens. Studies must be of adequate generation without the addition of antibiotics against atypical pathogens. Comparing the same studies may be impossible.

Correction for the baseline differences between patients given or not given atypical coverage in these studies may be impossible.

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