

Primary care

Effectiveness of β lactam antibiotics compared with antibiotics active against atypical pathogens in non-severe community acquired pneumonia: meta-analysis

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Abstract

Objective To systematically compare β lactam antibiotics with antibiotics active against atypical pathogens in the management of community acquired pneumonia.

Data sources Medline, Embase, Cochrane register of controlled trials, international conference proceedings, drug registration authorities, and pharmaceutical companies.

Review methods Double blind randomised controlled monotherapy trials comparing β lactam antibiotics with antibiotics active against atypical pathogens in adults with community acquired pneumonia. Primary outcome was failure to achieve clinical cure or improvement.

Results 18 trials totalling 6749 participants were identified, with most patients having mild to moderate community acquired pneumonia. The summary relative risk for treatment failure in all cause community acquired pneumonia showed no advantage of antibiotics active against atypical pathogens over β lactam antibiotics (0.97, 95% confidence interval 0.87 to 1.07). Subgroup analysis was undertaken in those with a specific diagnosis involving atypical pathogens. We found a significantly lower failure rate in patients with *Legionella* species who were treated with antibiotics active against atypical pathogens (0.40, 0.19 to 0.85). Equivalence was seen for *Mycoplasma pneumoniae* (0.60, 0.31 to 1.17) and *Chlamydia pneumoniae* (2.32, 0.67 to 8.03).

Conclusions Evidence is lacking that clinical outcomes are improved by using antibiotics active against atypical pathogens in all cause non-severe community acquired pneumonia. Although such antibiotics were superior in the management of patients later shown to have legionella related pneumonia, this pathogen was rarely responsible for pneumonia within the included trials. β lactam agents should remain the antibiotics of initial choice in adults with non-severe community acquired pneumonia.

Introduction

The optimal antibiotic therapy for community acquired pneumonia remains unclear. One of the barriers to better define treatment is the inability to accurately determine the part that the various micro-organisms play.¹ In only a few cases is the causative organism identified, due to the poor yield from routine microbiological tests. Since it was first identified in 1881, *Streptococcus pneumoniae* has been considered the major cause of community acquired pneumonia.² Its importance was supported by

the reduction in mortality observed after the introduction of sulphonamides³ and later β lactam antibiotics.⁴

With improvements in diagnostic microbiology, it became apparent that other organisms seemed causative in community acquired pneumonia. Three of the more recently recognised ones (*Mycoplasma pneumoniae*, *Legionella* species, and *Chlamydia pneumoniae*) are now associated with the term atypical pathogen. Their major distinguishing feature is a lack of in vitro response to β lactam and sulphonamide antibiotics, rather than any differences to pneumococcal pneumonia in clinical presentation.^{5 6}

The part that atypical organisms play and the need to provide specific antibiotic coverage for them in community acquired pneumonia is contentious. Recent guidelines vary.⁷⁻¹⁰ The single most important factor in this variance is the failure to produce level 1 evidence on which to base treatment recommendations. We carried out a meta-analysis to compare the efficacy of β lactam antibiotics with antibiotics active against atypical pathogens in adults with community acquired pneumonia to produce the level 1 evidence currently lacking.

Methods

We obtained relevant trials up to December 2003 from the Cochrane central register of controlled trials, Medline, and Embase using the broad search terms “explode pneumonia” and “explode antibiotic-agent” associated with standard limiters aimed to identify controlled trials. In addition we searched abstracts of conference proceedings, contacted registration authorities, searched the reference lists of review articles and retrieved studies, and contacted pharmaceutical companies that had carried out clinical trials on antibiotics active against atypical pathogens. We included studies regardless of date, language, or publication status.

Inclusion criteria were randomised double blind monotherapy trials comparing antibiotics active against atypical pathogens (fluoroquinolones, macrolides, and ketolides) with any β lactam antibiotic (penicillins and cephalosporins) in radiographically confirmed cases of community acquired pneumonia. The primary outcome of interest was failure to achieve clinical cure or improvement, as defined by each study. We excluded open label, non-comparative, and non-randomised studies owing to potential important bias from the subjective nature of the primary outcome variable. We also excluded studies with the



Details of the four unpublished studies are on [bmj.com](http://www.bmj.com)

option of adding an antibiotic active against atypical pathogens to β lactam therapy.

For the primary analysis we used the intention to treat or modified intention to treat populations (those with confirmed community acquired pneumonia who had received at least one dose of study drug). When both early and late end points were available, we used the earlier follow up time as the test of cure. We also reviewed the clinically evaluable per protocol population as well as all cause mortality. The criterion within each study report was used to define atypical pathogen diagnoses.

Data abstraction and quality

Two reviewers independently screened identified titles and abstracts without blinding to authorship or journal. Potentially relevant studies were obtained and the full text examined. All studies had complete blinding of investigators, participants, and outcome assessors thereby reducing the possibility of selection bias and detection bias. When important data were not reported, we contacted the author or pharmaceutical company that sponsored the study. Discrepancies between reviewers were resolved by discussion.

Study characteristics and quantitative data synthesis

We classified the studies by the name of the antibiotic active against atypical pathogens. Information was gathered for each study on participating countries, number of study sites, period (years) of study, study size, mean age, whether the intention to treat population was used for analysis, and the severity of the pneumonia (if available). Analysis was performed using meta-analytic software in Revman 4.2.3.

We expressed the results for the dichotomous outcome of failure to achieve clinical cure or improvement as relative risks with 95% confidence intervals. As there was no significant heterogeneity we pooled the data using the fixed effects model. Results were almost identical with the random effect model. We used a χ^2 test to analyse heterogeneity, and we considered a P value of 0.05 or less as significant. Subgroup analysis was undertaken on participants with atypical pathogen diagnoses.

Results

We screened over 2000 studies and retrieved over 100 potentially eligible ones. We identified 20 studies that met our inclusion criteria.¹¹⁻²⁶ Four of the studies (30% of participants) were unpublished as at November 2004 and were obtained from the sponsoring pharmaceutical companies either directly or secondary to the finding of a conference proceedings (see bmj.com). Two small studies concerned children.^{11 12} We decided to exclude these from our meta-analysis given the distinct clinical context. Three blinded studies were also excluded, as the protocol included the option of adding an agent active against atypical pathogens to the β lactam therapy.²⁷⁻²⁹

The 18 included trials were carried out in more than 30 countries between 1980 and 2000 and included 6749 analysable participants (table). Overall, the trials used nine different fluoroquinolones, two macrolides, and one ketolide. Most study drugs were given orally, with only two of the earlier studies using intravenous therapy initially. Most of the studies listed specific exclusion criteria; a standard feature in most trials of community acquired pneumonia sponsored by pharmaceutical companies. Common exclusions included the requirement for parenteral antimicrobials at study entry in trials of oral antibiotics, hospital acquired or aspiration pneumonia, immunocompromised patients, and major hepatic or renal dysfunction. The specific inclusion and exclusion criteria resulted in participants who

were younger and with a better prognostic risk profile than observational pneumonia cohorts.³⁰

Primary outcome of interest

All trials reported the proportion of patients who failed to achieve clinical cure or improvement, an overall rate of 18%. We found no significant difference between treatments in any study or significant heterogeneity between studies. From a combined analysis of the studies (fig 1) we found no evidence that antibiotics active against atypical pathogens were superior to β lactam antibiotics (relative risk 0.97, 95% confidence interval 0.87 to 1.07). The same conclusion was drawn from separate analyses of the studies on macrolides and ketolides (0.81, 0.58 to 1.14) and fluoroquinolones (0.99, 0.88 to 1.11). We also compared the relative risk of the 10 published studies on fluoroquinolones (0.90, 0.77 to 1.04) with the four unpublished studies on fluoroquinolones (1.15, 0.96 to 1.37).

We analysed the data on all cause mortality separately; 130 deaths were reported (mortality 1.9%). We observed no differences in mortality between the study arms (relative risk 1.20, 0.84 to 1.71). This low mortality is in keeping with most patients having mild to moderate (non-severe) community acquired pneumonia.

Fifteen of the trials provided data on either the intention to treat population or the modified intention to treat population. Three studies reported only on the clinically evaluable population, although the overall dropout rate was less than 17%.^{13 18 26} As all the studies were blinded, we did not consider the lack of intention to treat data in these three studies as critical and we therefore included the data. The treatment effect (relative risk 0.97) was not altered when we excluded trials that did not use an intention to treat or modified intention to treat method. Similar results (0.93, 0.81 to 1.06) were obtained from a separate analysis on the clinically evaluable per protocol population (n = 5639), with the failure to achieve clinical cure or improvement reduced to 13%.

We decided to include one study (weighting 3.3%) where a small proportion (< 10%) of patients had nosocomial pneumonia.¹⁴ The result was not altered (relative risk 0.97) when we carried out a sensitivity analysis with these data excluded. The time point for assessment varied between studies. Sixteen of the studies had visits for end of treatment or for test of cure within 10 days of completion of the study drug, whereas two studies assessed patients at the end of follow up. We found no evidence of a secular trend of decreasing treatment effect in the β lactam arms, suggesting that there was no impact on treatment effect from the worldwide trend for increasing pneumococcal resistance.

Subgroup analysis

Overall, 311 patients (13 studies) were diagnosed as having *M pneumoniae*, 115 (seven studies) as having *C pneumoniae*, and 75 (10 studies) as having *Legionella* species (fig 2). We found no significant treatment effect in patients with *M pneumoniae* (relative risk 0.60, 0.31 to 1.17) or *C pneumoniae* (2.32, 0.67 to 8.03). In contrast, the failure rate from antibiotics active against atypical pathogens in patients with legionella was statistically lower (0.40, 0.19 to 0.85).

Discussion

Data from our meta-analysis do not support the need for antibiotics that possess specific activity against atypical pathogens in the initial management of adults with mild to moderate community acquired pneumonia. A major strength of our study was the

Characteristics of included studies comparing β lactam antibiotics with antibiotics active against atypical pathogens in patients with community acquired pneumonia

| Study drug | Reference, country | No of sites; year | Participants | Intention to treat | Intervention | Time of outcome assessment |
|------------------------------|--|-------------------|--|--------------------|--|---------------------------------|
| Azithromycin | Kinasewitz 1991 ¹³ , United States | 28; pre-1990 | Adults (mean age 41); 119 randomised; 71 clinically analysable | Not available | Azithromycin for 5 days versus cefaclor for 10 days | Days 10-13 |
| Ciprofloxacin | Johnson 1996 ¹⁴ , United States | 19; 1990-3 | Adults (mean age 59); about 90% had community acquired pneumonia; 217 randomised | 217 patients | Intravenous ciprofloxacin versus intravenous ceftriaxone for 3-10 days | 0-7 days after end of treatment |
| Erythromycin | Macfarlane 1983 ¹⁵ , United Kingdom | One; 1980-1 | Adults (mean age 50); 122 randomised | 91 patients* | Intravenous erythromycin followed by oral erythromycin versus intravenous ampicillin followed by oral amoxicillin for 7 days | Day 13 |
| Gatifloxacin | Lode 2004 ¹⁶ , multinational | 73; 1997-8 | Adults (mean age 50); 462 randomised | 456 patients* | Gatifloxacin versus combined amoxicillin and clavulanic acid for 5-10 days | 1-3 days after end of treatment |
| Gatifloxacin | Study report 2000 (KF5501/16; see bmj.com), multinational | 123; 1999-2000 | Adults (mean age 52); 1061 randomised; 34% had severe community acquired pneumonia | 1051 patients* | Gatifloxacin versus amoxicillin for 7-10 days | Days 10-17 |
| Gemifloxacin | Leophonte 2004 ¹⁷ , multinational | 102; 1998-9 | Adults (mean age 54); 324 randomised; 16% had severe community acquired pneumonia | 320 patients* | Gemifloxacin versus combined amoxicillin and clavulanic acid for 7-10 days | Days 12-14 |
| Grepafloxacin | O'Doherty 1997 ¹⁸ , United Kingdom and Eire | 43; 1992-3 | Adults (mean age 55); 264 randomised; 225 clinically analysable | Not available | Grepafloxacin versus amoxicillin for 7-10 days | Days 28-42 |
| Grepafloxacin | Study report 1997 (106-92-201; see bmj.com); United States, United Kingdom, Eire | 83; 1992-6 | Adults; (mean age unavailable); 475 randomised | 475 patients | Grepafloxacin versus cefaclor for 7-10 days | Days 28-42 |
| Grepafloxacin | Study report 1999 (GFXB 3004; see bmj.com); multinational | 70; 1996-8 | Adults (median age 52); 370 randomised | 370 patients | Grepafloxacin versus amoxicillin for 10 days | 1-3 days after end of treatment |
| Levofloxacin | Study report 1994 (DR-3355/E05; see bmj.com); Europe | 40; 1992-3 | Adults (median age 61); 140 randomised; 16% had severe community acquired pneumonia | 123 patients* | Levofloxacin (two different doses) versus amoxicillin for 7-14 days | 0-2 days after end of treatment |
| Levofloxacin | Carbon 1999 ¹⁹ ; multinational | 50; pre-1996 | Adults (mean age 41); 516 randomised | 516 patients | Levofloxacin (two different doses) versus combined amoxicillin and clavulanic acid for 7-10 days | 2-5 days after end of treatment |
| Moxifloxacin | Petitpretz 2001 ²⁰ ; multinational | 84; 1997-8 | Adults (mean age 51); 411 randomised | 408 patients* | Moxifloxacin versus amoxicillin for 10 days | 3-5 days after end of treatment |
| Sparfloxacin or erythromycin | Lode 1995 ²¹ ; multinational | 124; 1990-2 | Adults (mean age 54); 808 randomised | 808 patients | Sparfloxacin versus erythromycin versus combined amoxicillin and clavulanic acid for 7-14 days; randomised 2:1:1 | Days 7-14 |
| Sparfloxacin | Aubier 1998 ²² ; France, South Africa, Switzerland | 55; 1991-2 | Adults (mean age 42); 329 randomised | 329 patients | Sparfloxacin versus amoxicillin for 10-14 days | Days 14-21 |
| Sparfloxacin | Donowitz 1997 ²³ ; United States | 74; 1992-5 | Adults (mean age 49); 330 randomised | 330 patients | Sparfloxacin versus cefaclor for 10 days | Days 17-23 |
| Telithromycin | Hagberg 2002 ²⁴ ; multinational | 59; 1998-9 | Adults (median age 42); 404 randomised; 27% had prognostic severity index score ≥ 3) | 404 patients | Telithromycin versus amoxicillin for 10 days | Days 17-21 |
| Temafloxacin | Carbon 1992 ²⁵ ; France | 27; 1989-90 | Adults (mean age 55); 246 randomised | 243 patients* | Temafloxacin versus amoxicillin for 10 days | 1-3 days after end of treatment |
| Trovafloxacin | Tremolieres 1998 ²⁶ ; multinational | 44; 1995-6 | Adults (mean age 52); 342 randomised; 312 clinically analysable | Not available | Trovafloxacin versus amoxicillin for 7-10 days | Days 7-10 |

*Modified intention to treat analysis.

inclusion of only randomised prospective double blinded studies, thus appreciably avoiding bias. Although the patients were mostly recruited from hospital settings, the use of orally based regimens by many of the studies resulted in fewer patients with severe pneumonia. This is reflected by the low mortality. We are therefore not able to provide any guidance for the management of severe community acquired pneumonia, where the standard of care is currently intravenous antibiotic therapy.⁷

Despite this, our results are valuable in guiding the management of many adults with community acquired pneumonia.

Although mortality is far more likely to occur in those with severe pneumonia as classified by prognostic indices for community acquired pneumonia, a large proportion (42% in the US derivation study³⁰ and 53% in the international derivation study³¹) of admissions to hospital are patients with mild to moderate pneumonia (prognostic index scores 1-3). Mortality in patients admitted with prognostic index scores between 1 and 3 is 1.5%,³⁰ similar to the rate seen in our study. In addition, most patients who remain in the primary care setting also have mild to moderate pneumonia.

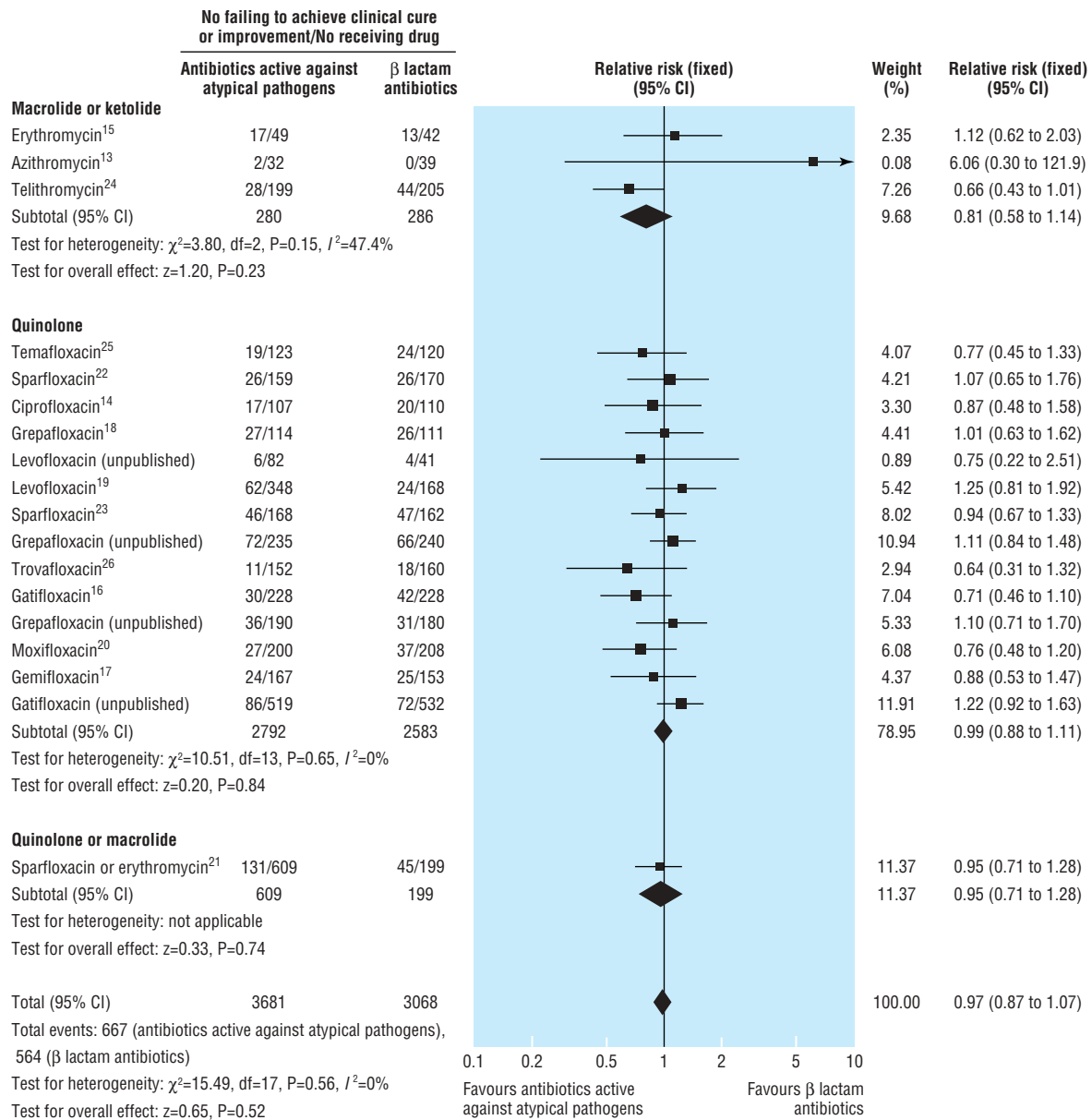


Fig 1 Number of patients failing to achieve clinical cure or improvement with β lactam antibiotics compared with antibiotics active against atypical pathogens in all cause community acquired pneumonia

We believe that our study has sufficient power to address adequately the study question, as reflected by the narrow confidence interval for relative risk (0.97, 0.87 to 1.07). If a relative risk of 0.97 was the true magnitude of benefit from using antibiotics active against atypical pathogens compared with β lactam antibiotics, then the number needed to treat of 185 for preventing one extra failure would not be seen as valuable by most respiratory physicians. This is particularly true when clinical failure may only indicate a slower time to resolution of symptoms, rather than severe morbidity or mortality.

The antibiotics active against atypical pathogens we reviewed were fluoroquinolones, macrolides, and ketolides. These agents have excellent in vitro activity against each of the three atypical organisms considered to cause community acquired pneumonia, with most having good coverage against *S pneumoniae*. The studies compared β lactam antibiotics in a variety of forms (cephalosporins, narrow spectrum penicillins, and combinations of β lactam and β lactamase inhibitor), which all lack activity against atypical pathogens. We chose to include studies on anti-

biotics no longer in general usage. Grepafloxacin, sparfloxacin, trovafloxacin, and temifloxacin are no longer actively marketed owing to their side effect profiles rather than lack of efficacy. The clinical response rates for these fluoroquinolones were no different from those currently approved by the US Food and Drug Administration (levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin).

In addition to looking at the results for all cause community acquired pneumonia, we reviewed specific therapeutic responses in patients whose pneumonia was considered to be related to the three atypical organisms. In total, 501 of the patients enrolled in these studies were diagnosed as having atypical pathogens. Each study defined the specific criteria on which these diagnoses were made although there was variability as to whether all, some, or none of the atypical organisms were sort after. Serology, the basis for nearly all of the diagnoses of atypical pathogens in the included studies, has the major drawbacks of variable sensitivity and specificity.³² As a result the diagnoses are uncertain, highlighting one of the reasons that the role of atypical

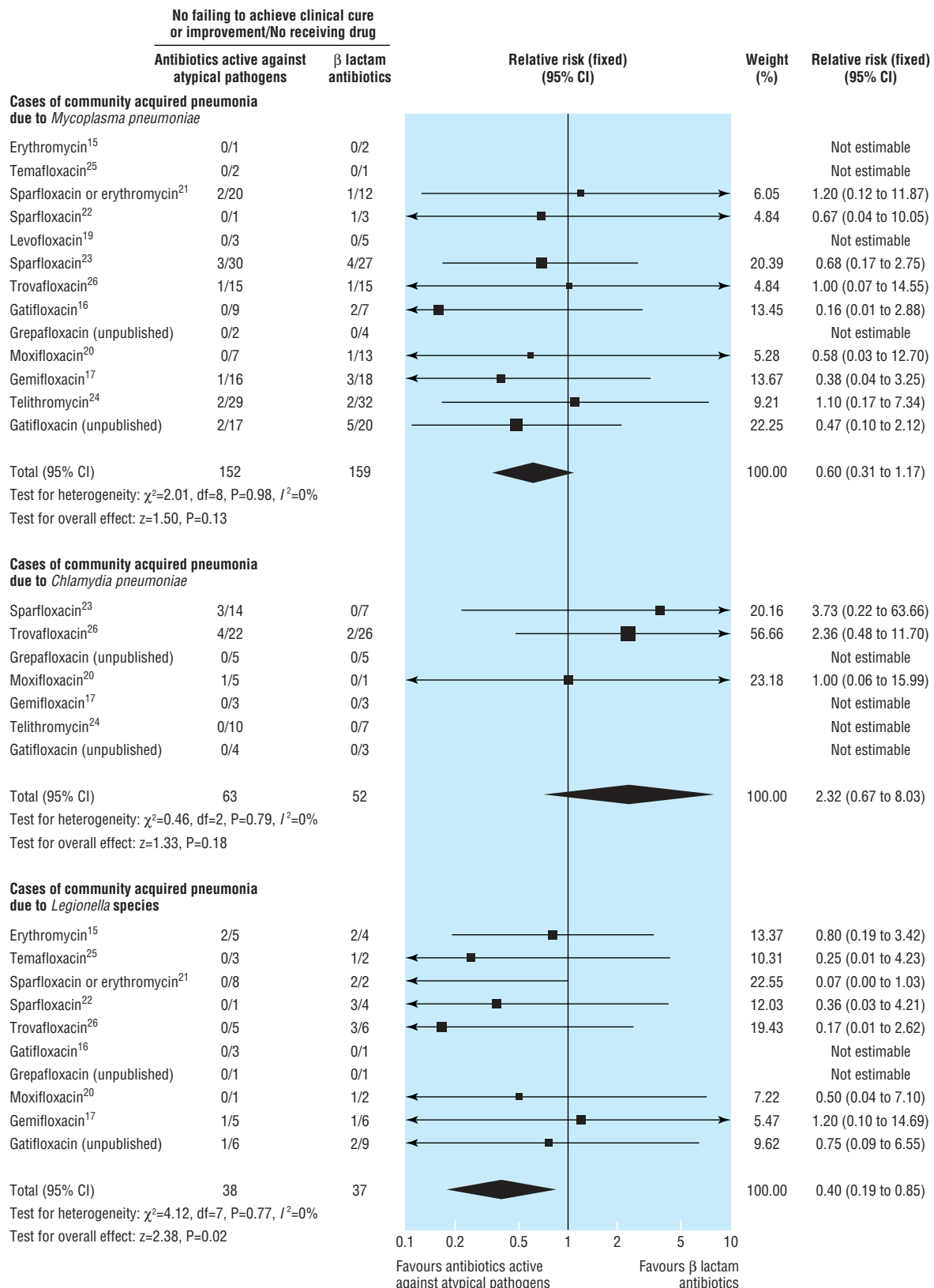


Fig 2 Number of patients failing to achieve clinical cure or improvement with β lactam antibiotics compared with antibiotics active against atypical pathogens in confirmed cases of community acquired pneumonia related to *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species

pathogens has remained controversial. When antibiotics active against atypical pathogens were used, only pneumonia related to legionella showed a statistically significant improvement in outcome. This organism is uncommon (< 3%) in mild to moder-

ate community acquired pneumonia.^{1 33} Our data suggest that coverage for the possibility of legionella is not warranted in the initial management of non-severe community acquired pneumonia.

Given the lack of in vitro activity of β lactam antibiotics, our finding of similar outcomes for *M pneumoniae* and *C pneumoniae* was unanticipated. Although confidence intervals were wide, we do not believe that lack of power necessarily explains these results, as the number of diagnoses were not small (311 and 115 patients for *M pneumoniae* and *C pneumoniae*, respectively), and failure rates were low (<10%). Despite legionella being diagnosed on fewer occasions, differences in outcome were readily apparent, in contrast to *M pneumoniae* and *C pneumoniae*. Alternative explanations for our findings include incorrect diagnoses, self limiting infections, or asymptomatic infections associated with a coinfecting pathogen responsive to β lactam antibiotics. Each of these explanations is conceivable given the diagnostic difficulties, the reported high rate of atypical coinfections,³⁴ and the ability to culture *C pneumoniae* from asymptomatic individuals.³⁵⁻³⁷ Another explanation is that using a specific time point to assess clinical outcome might have missed a more rapid response in one arm. Data on time to resolution of symptoms or length of hospital stay were, however, not available to us. Based on the low failure rates in both treatment arms and the lack of a significant treatment difference within the included studies, we suggest that the role of *M pneumoniae* and *C pneumoniae* in community acquired pneumonia may have been overplayed.

Several questions need to be asked before our findings can be extrapolated. Firstly, were the patients (over 6700) in our meta-analysis similar to cohorts with pneumonia not entered into clinical trials? As indicated there is a trend to inclusion of younger patients than seen in prospectively enrolled observational cohorts. In addition, because many of the studies used oral therapy, most of the patients had non-severe community acquired pneumonia. Therefore, although our data are only applicable to a subset of patients with community acquired pneumonia, this subset makes up a major proportion of patients with pneumonia. Our findings are at variance with the American Thoracic Society guidelines, which state that all populations with community acquired pneumonia should be treated for possible infection with atypical pathogens⁷; but our findings agree with the British Thoracic Society guidelines.¹ The British guidelines consider *S pneumoniae* the most important target of initial antibiotic therapy and state that a policy aiming to always cover the atypical pathogens is inappropriate.

Although some may see the inclusion of unpublished material as a limitation in our study, we believe that it is a notable strength. It is unsurprising that four studies sponsored by the pharmaceutical industry (30% of the included patients) have not been published, given their rather unflattering treatment effect compared with the older, often out of patent, β lactam antibiotics.

Our results provide the best level of evidence currently available addressing the necessity for coverage of atypical pathogens in the initial management of community acquired pneumonia. In 2003, Oosterheert et al contended that data did not support the routine addition of macrolides or monotherapy with fluoroquinolones as standard care for patients admitted to hospital with community acquired pneumonia.³⁸ The Swedish Infectious Diseases Society also suggested that the role of atypical pathogens might have been overestimated within current guidelines.³⁹ Our results strongly support both these assertions. We have reviewed only initial therapy in this meta-analysis and emphasise that antibiotic treatment should always be reassessed in any patient who shows signs of deterioration or failure to improve. Guidelines based on retrospective studies⁴⁰⁻⁴¹ should always be deemed inferior to level 1 evidence because it is

What is already known on this topic

Recommendations for antibiotic treatment of community acquired pneumonia are based on expert opinion and in vitro data rather than data from clinical trials

North American and European guidelines vary as to whether initial antibiotic regimens should always include coverage for the atypical organisms *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, and *Legionella* species

What this study adds

Evidence is lacking that antibiotics active against atypical pathogens improve clinical outcomes in adults with non-severe community acquired pneumonia

β lactam antibiotics were not inferior to antibiotics active against atypical pathogens in patients with community acquired pneumonia related to *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*

β lactam agents should remain the antibiotics of choice in the initial management of mild to moderate community acquired pneumonia, as currently advocated by the British Thoracic Society

impossible to control for the reasons why certain antibiotics are prescribed. The British Thoracic Society has astutely summed up the current situation: "There is clearly variation in medical practice with regard to licensing, availability, choice, dose, route of administration, and duration of treatment which is more a reflection of local custom and practice than robust scientific evidence."¹

In conclusion, our meta-analysis provides level 1 evidence contrary to the current American Thoracic Society guidelines for patients with community acquired pneumonia.⁷ Although we have confirmed the importance of specific therapy when legionella is confirmed, evidence is lacking that specific therapy is required for *M pneumoniae* or *C pneumoniae*. β lactam antibiotics should remain the initial choice in the management of non-severe community acquired pneumonia in adults given our results, the benefits of using narrower spectrum agents, and the cost advantages.

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Ethical approval: Not required.

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