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 microorganisms play.[1] Since it was first identified in 1881, *Streptococcus pneumoniae* has been considered the major cause of community acquired pneumonia.[2] With improvements in diagnostic microbiology, it became apparent that other organisms also seemed causative. 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.

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.[1 3–6] The single most important factor in this variance is the failure to produce level 1 evidence on which to base treatment recommendations.

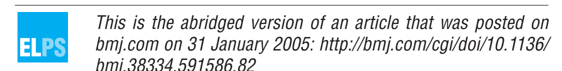
We carried out a meta-analysis to compare the efficacy of β lactam antibiotics with antibiotics active against atypical pathogens in adults with community acquired pneumonia to produce the level 1 evidence currently lacking.

Methods

We obtained relevant trials up to December 2003 from the Cochrane central register of controlled trials, Medline, and Embase. 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.

We included randomised double blind monotherapy trials comparing antibiotics active against atypical pathogens (fluoroquinolones, macrolides, and

Details of the four unpublished studies are on bmj.com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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.

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). We used the earliest follow up times 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. As to whether all, some, or none of the atypical organisms were sort after varied.

Data abstraction and quality

Two reviewers independently screened identified titles and abstracts. All studies had complete blinding of investigators, participants, and outcome assessors. When important data were not reported, we contacted the author or pharmaceutical company that sponsored the study.

Study characteristics and quantitative data synthesis

We classified the studies by the name of the antibiotic active against atypical pathogens. The information gathered from each study is listed on bmj.com.

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. 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 identified 20 studies that met our inclusion criteria.[7–22] Four have not been published (see bmj.com). We excluded two small studies concerning children.[7 8] Three blinded studies where the protocol allowed the addition of an agent active against atypical pathogens to the β lactam therapy were not included.[23–25]

The 18 included trials comprised 6749 analysable participants (see table on bmj.com). The trials used nine different fluoroquinolones, two macrolides, and one ketolide. Most study drugs were given orally. Common exclusions are listed on bmj.com. The specific inclusion and exclusion criteria resulted in participants who were younger and with a better prognostic risk profile than observational pneumonia cohorts.[26]

Primary outcome of interest

All trials reported the proportion of patients who failed to achieve clinical cure or improvement. We found no significant difference between treatments in any study or significant heterogeneity between studies. From a combined analysis of the studies (figure) 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. We observed no differences in mortality between the study arms (relative risk 1.20, 0.84 to 1.71).

Fifteen 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.[9 14 22] The treatment effect (relative risk 0.97) was not altered when we excluded trials that did not use an intention to treat method or the 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 from 18% to 13%.

The time point for assessment varied between studies—16 used visits for end of treatment or for test of cure within 10 days of completion of the study drug, whereas two studies used the end of follow up.

Subgroup analysis

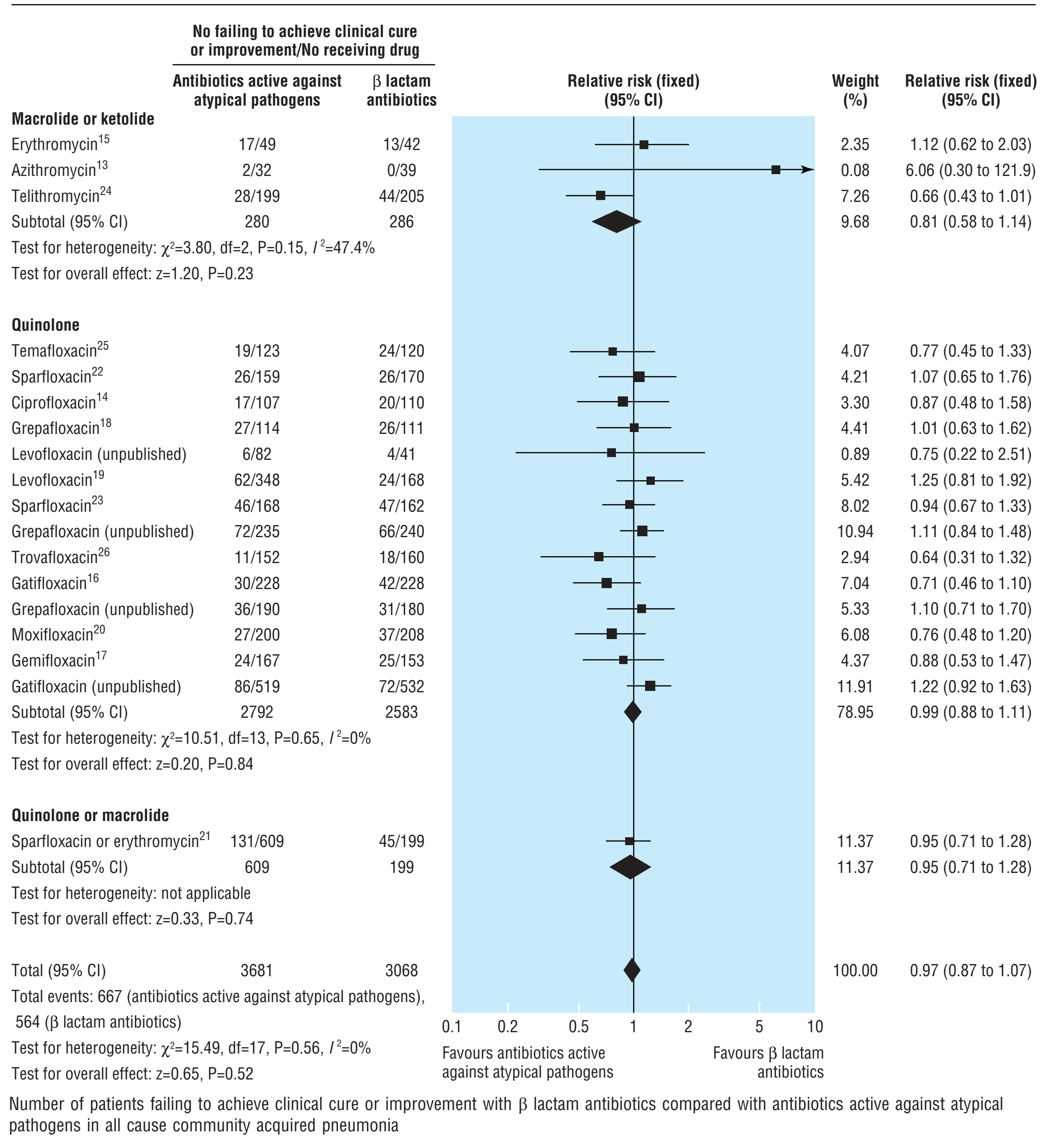
We found no significant treatment effect in patients with *M pneumoniae* (relative risk 0.60, 0.31 to 1.17) or *C pneumoniae* (2.32, 0.67 to 8.03). In contrast, the failure rate from antibiotics active against atypical pathogens in patients with legionella was statistically lower (0.40, 0.19 to 0.85).

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 inclusion of only randomised prospective double blinded studies, thus avoiding bias. 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.[3]

Our results are valuable, however, in guiding the management of many adults with community acquired pneumonia. Although mortality is more likely to occur in those with severe pneumonia, a large proportion of admissions to hospital are patients with mild to moderate pneumonia, with a mortality similar to that in our study (1.5%).[26]

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, which all lack activity against atypical pathogens.



	No failing to achieve clinical cure or improvement/No receiving drug: Antibiotics active against atypical pathogens	β lactam antibiotics	Weight (%)	Relative risk (fixed) (95% CI)
Macrolide or ketolide				
Erythromycin[15]	17/49	13/42	2.35	1.12 (0.62 to 2.03)
Azithromycin[13]	2/32	0/39	0.08	6.06 (0.30 to 121.9)
Telithromycin[24]	28/199	44/205	7.26	0.66 (0.43 to 1.01)
Subtotal (95% CI)	280	286	9.68	0.81 (0.58 to 1.14)
Test for heterogeneity: χ^2=3.80, df=2, P=0.15, I^2=47.4%				
Test for overall effect: z=1.20, P=0.23				
Quinolone				
Temafloxacin[25]	19/123	24/120	4.07	0.77 (0.45 to 1.33)
Sparfloxacin[22]	26/159	26/170	4.21	1.07 (0.65 to 1.76)
Ciprofloxacin[14]	17/107	20/110	3.30	0.87 (0.48 to 1.58)
Grepafloxacin[18]	27/114	26/111	4.41	1.01 (0.63 to 1.62)
Levofloxacin (unpublished)	6/82	4/41	0.89	0.75 (0.22 to 2.51)
Levofloxacin[19]	62/348	24/168	5.42	1.25 (0.81 to 1.92)
Sparfloxacin[23]	46/168	47/162	8.02	0.94 (0.67 to 1.33)
Grepafloxacin (unpublished)	72/235	66/240	10.94	1.11 (0.84 to 1.48)
Trovafloxacin[26]	11/152	18/160	2.94	0.64 (0.31 to 1.32)
Gatifloxacin[16]	30/228	42/228	7.04	0.71 (0.46 to 1.10)
Grepafloxacin (unpublished)	36/190	31/180	5.33	1.10 (0.71 to 1.70)
Moxifloxacin[20]	27/200	37/208	6.08	0.76 (0.48 to 1.20)
Gemifloxacin[17]	24/167	25/153	4.37	0.88 (0.53 to 1.47)
Gatifloxacin (unpublished)	86/519	72/532	11.91	1.22 (0.92 to 1.63)
Subtotal (95% CI)	2792	2583	78.95	0.99 (0.88 to 1.11)
Test for heterogeneity: χ^2=10.51, df=13, P=0.65, I^2=0%				
Test for overall effect: z=0.20, P=0.84				
Quinolone or macrolide				
Sparfloxacin or erythromycin[21]	131/609	45/199	11.37	0.95 (0.71 to 1.28)
Subtotal (95% CI)	609	199	11.37	0.95 (0.71 to 1.28)
Test for heterogeneity: not applicable				
Test for overall effect: z=0.33, P=0.74				
Total (95% CI)	3681	3068	100.00	0.97 (0.87 to 1.07)
Total events: 667 (antibiotics active against atypical pathogens), 564 (β lactam antibiotics)				
Test for heterogeneity: χ^2=15.49, df=17, P=0.56, I^2=0%				
Test for overall effect: z=0.65, P=0.52				

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

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. Serology, however, the basis for nearly all of the diagnoses of atypical pathogens in the included studies, has the major drawbacks of variable sensitivity and specificity.[27] As a result the diagnoses are uncertain, highlighting one of the reasons that the role of atypical 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 in non-severe community acquired pneumonia.[1 28] Our data suggest that coverage for the possibility of legionella is not warranted in the initial management of non-severe community acquired pneumonia.

Despite legionella being diagnosed on fewer occasions, differences in outcome were readily apparent, in contrast to *M pneumoniae* and *C pneumoniae*. We do not believe that a lack of power is the most likely explanation for our results. Alternative explanations for our findings include incorrect diagnoses, self limiting infections, or asymptomatic infections associated with coinfecting pathogens responsive to β lactam antibiotics. Each of these explanations is conceivable given the diagnostic difficulties, the reported high rate of atypical coinfections,[29] and the ability to culture *C pneumoniae* from asymptomatic individuals.[30–32] 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 in our meta-analysis similar to cohorts with pneumonia

What is already known on this topic

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

North American and European guidelines vary as to whether initial antibiotic regimens should include coverage for atypical pathogens

What this study adds

There is no evidence 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 non-severe community acquired pneumonia, as currently advocated by the British Thoracic Society

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[3] but agree with the British Thoracic Society guidelines, which 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.[1]

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. We have only reviewed 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 studies should always be deemed inferior to level 1 evidence because it is impossible to control for the reasons why certain antibiotics are prescribed. We provide level 1 evidence contrary to the current American Thoracic Society guidelines for patients with community acquired pneumonia.[3] 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*.

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Contributors: See bmj.com

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Ethical approval: Not required.

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Commentary: A step forward in the everyday management of adults with community acquired pneumonia

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Few topics cause such fierce discussion among doctors as does the antimicrobial treatment of lower respiratory tract infections. The meta-analysis by Mills et al is a valuable contribution to these debates.[1] Their study should reassure all health professionals who routinely manage non-severe community acquired pneumonia that therapy using oral β lactam antibiotics, macrolides, or fluoroquinolones is equally effective when judged by clinical cure and mortality. Although other relevant outcomes such as speed of response, subsequent relapse rates, and harmful antibiotic effects were not assessed, the findings and the different cost and side effect profile of these agents means that a β lactam antibiotic (with macrolides and tetracyclines as good alternatives in individuals who are hypersensitive to penicillin) should usually remain the preferred therapy for patients with non-severe community acquired pneumonia managed in the community or in hospital. This is supported by data from clinical practice (as opposed to clinical trials) in Sweden.[2] Furthermore, the similar outcome in conventional and atypical pathogens supports the view that distinction of these causes using microbiological tests is likely to be unhelpful in this patient group.[3]

Of course it remains possible that in special settings with a much higher atypical incidence or resistance rate (only 7% of cases included by Mills et al had confirmed infection by atypical organisms and bacterial resistance rates were not provided) these findings do not apply. That so many patients from over 30 different countries were included in the study, however, means that these findings are likely to be widely relevant. Elderly patients were poorly represented, but they usually have a lower rate of infection with atypical bacteria.[4] One situation where a β lactam antibiotic would not be first choice is when legionella infection is suspected. Such infection is, however, unusual in the community.[4]

One question that remains is which β lactam antibiotic to use. In 14 of the 18 studies either amoxicillin or amoxicillin-clavulanate was used as a comparator. As oral cephalosporins have poor pharmacokinetics it would seem that amoxicillin or amoxicillin-clavulanate should usually be the first choice for therapy. It should, however, be realised that side effects are more common with amoxicillin-clavulanate and that penicillinase producing *Haemophilus influenzae* is an uncommon cause of mild community acquired pneumonia.

Most studies on antimicrobial treatment in community acquired pneumonia include only patients in whom the condition has been radiographically confirmed. In instances of lower respiratory tract infection in primary care, chest radiography is not carried out.[5] Detection of community acquired pneumonia by clinical methods is neither sensitive nor specific, but a benefit of chest radiography in selected patients with lower respiratory tract infections has not been shown either, or tested. It would seem reasonable to apply these research findings to patients with suspected (rather than confirmed) community acquired pneumonia on the basis of specific features such as focal chest signs, dyspnoea or tachypnoea, or prolonged fever. Use of a β lactam antibiotic in patients with suspected or definite community acquired pneumonia will pose only a limited—and thus acceptable—risk for the development of bacterial resistance.

In the absence of any single adequately powered comparative antibiotic study, Mills et al's meta-analysis provides strong evidence to support the everyday management of adults with community acquired pneumonia.

Competing interests: MW has received travel expenses and lecture fees from several manufacturers of macrolide and fluoroquinolone antibiotics, including GlaxoSmithKline, Bayer, and Pfizer. TJMV has received travel expenses from GlaxoSmithKline.

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