Gemifloxacin for the treatment of community-acquired pneumonia and acute exacerbation of chronic bronchitis: a meta-analysis of randomized controlled trials

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CRD summary
This review concluded that the effectiveness of gemifloxacin was equivalent or superior to that of other antibiotics for community-acquired pneumonia and acute exacerbations of chronic bronchitis. However, there was significantly higher risk of rash and diarrhoea compared to other quinolones. Limitations in the evidence base and data analysis suggest that these conclusions should be regarded as provisional.

Authors' objectives
To evaluate the effectiveness and safety of gemifloxacin for community-acquired pneumonia and acute exacerbation of chronic bronchitis.

Searching
PubMed, EMBASE, Chinese Biomedical Literature Database and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched to June 2010, with no language restrictions; search terms were reported. Relevant articles and reviews were handsearched for additional studies. Abstracts of conference presentations were not searched.

Study selection
Randomised controlled trials (RCTs) were eligible if they compared gemifloxacin with other quinolones, or combination therapy with macrolides and β-lactams, or monotherapy with macrolide ketolide or β-lactam alone, for the treatment of community-acquired pneumonia, acute exacerbation of chronic bronchitis or acute exacerbation of chronic obstructive pulmonary disease. Trials could be both blinded and unblinded. Studies had to assess the effectiveness, toxicity and/or mortality of both treatments. Both clinical and microbiological outcomes were eligible. Trials that focused on pharmacokinetic or pharmacodynamic profiles were excluded.

The primary outcomes (using an intention-to-treat analysis) were: all-cause mortality during the treatment and follow-up period; treatment success for clinically evaluable populations; and adverse events possibly related to study antibiotics. Treatment success (or cure) was defined in the paper. Effectiveness was measured at the test-of-cure visit. Secondary outcomes included: withdrawals due to drug-related events; microbiological assessment; eradication (documented or presumed) of *H. influenzae*, *S. pneumoniae*, *M. catarrhalis* and atypical pathogens (including *M. pneumoniae*, *C. pneumoniae* and *Legionella* species).

Oral gemifloxacin at 320mg/day was the dosage in all studies, for seven to 14 days for community-acquired pneumonia, and for five days for most studies of acute exacerbation of chronic bronchitis. Gemifloxacin was compared to: other quinolones (oral levofloxacin; oral trovafloxacin); and β-lactams and/or macrolides (ceftriaxone followed by oral cefuroxime; oral amoxicillin/clavulanate; and oral clarithromycin). Regimen details were given. Administration of antibiotics prior to study enrolment or additional antibiotics during the trials was not allowed but one control group was given a macrolide. Most studies were of acute exacerbation of chronic bronchitis patients; one RCT was of both community-acquired pneumonia and acute exacerbation of chronic bronchitis patients; and 30% studies were of community-acquired pneumonia patients alone. All studies were of adult patients; patient age ranged from 18 to 67 years, where stated.

Two independent reviewers performed the study selection.

Assessment of study quality
Methodological quality assessment was performed using a modified Jadad score. One point was given for each of five criteria: randomisation; random number generation; double-blinding procedure details; withdrawals information; and concealment of allocation. High quality RCTs scored 3 to 5 points and low quality RCTs scored 2 points or fewer.

Two independent reviewers carried out quality assessment.
Data extraction
Two independent reviewers performed the data extraction using a predefined checklist; discrepancies were resolved by consensus or referral to a third reviewer. The numbers of participants and events in each group were used to calculate odds ratios (OR) with 95% confidence intervals.

Methods of synthesis
Results were pooled using a fixed-effect model (Mantel-Haenszel) if there was no significant heterogeneity, a random-effects model (Der Simonian-Laird) was used where there was significant heterogeneity, to give odds ratios with 95% confidence intervals. Between-study heterogeneity was determined using $I^2$ and $X^2$; $p<0.10$ indicated significant heterogeneity. Sensitivity analyses were performed that compared gemifloxacin with other quinolones and with β-lactams and/or macrolides and for community-acquired pneumonia and acute exacerbation of chronic bronchitis patients separately. Meta-analyses were performed for intention-to-treat populations and separately for treatment success for clinically evaluable populations, where suitable data was available. Sensitivity analyses by study quality were also performed for clinically evaluable populations. Publication bias was assessed using Egger's Test and visually using funnel plots.

Results of the review
Ten RCTs were identified (3,940 patients, range 33 to 712). Mean Jadad score was 3.1, range 2 to 4, with eight high quality studies and two low quality studies. Results were generally given for an intention-to-treat analysis and mainly for a fixed-effect analysis, unless stated otherwise.

Treatment success
Significantly higher treatment success for gemifloxacin versus other antibiotics (OR 1.39, 95% CI 1.15 to 1.68; $I^2=11%$; eight studies). Clinical success was also significantly higher for gemifloxacin versus other quinolones (OR 1.69, 95% CI 1.28 to 2.23; $I^2=0%$; five studies) but not for gemifloxacin versus β-lactams and/or macrolides (OR 1.16, 95% CI 0.89 to 1.50; $I^2=43%$; three studies). Results did not change when they were calculated for clinically evaluable populations. An intention-to-treat analysis found treatment success was higher for gemifloxacin versus other antibiotics for the two subsets of diseases (OR 1.37, 95% CI 1.03 to 1.83; $I^2=18%$; four studies for community-acquired pneumonia; and OR 1.40, 95% CI 1.09 to 1.80; $I^2=28%$; five studies for acute exacerbation of chronic bronchitis) but the results were not significant when they were calculated for clinically evaluable populations.

All-cause mortality
There were no significant differences in all-cause mortality for gemifloxacin versus other antibiotics, versus other quinolones, or versus β-lactams and/or macrolides.

Adverse events
For gemifloxacin versus other quinolones, there were no significant differences in total adverse events (OR 0.89, 95% CI 0.56 to 1.41; $I^2=63%$; four studies) or nausea for gemifloxacin versus other quinolones. However, patients experienced significantly more diarrhoea (OR 2.01, 95% CI 1.00 to 4.06; $I^2=0%$; three studies) and rash (OR 2.66, 95% CI 1.03 to 6.87; $I^2=0%$; two studies) with gemifloxacin.

For gemifloxacin versus β-lactams and/or macrolides, there were significantly lower total adverse events (OR 0.71, 95% CI 0.57 to 0.89; $I^2=41%$; five studies) for gemifloxacin versus β-lactams and/or macrolides, including diarrhoea (OR 0.47, 95% CI 0.32 to 0.69; $I^2=51%$; five studies). There were higher rates of nausea and rash ($I^2=0%$; three studies) for gemifloxacin but the effects were not significant.

There were no significant differences between gemifloxacin and comparators for microbiological outcomes. Results of sensitivity analyses were reported. A funnel plot indicated that there was no significant publication bias.

Authors' conclusions
The available evidence suggested that gemifloxacin 320mg oral daily was equivalent or superior to other approved antibiotics in effectiveness and safety for community-acquired pneumonia and acute exacerbation of chronic bronchitis but rash was a potential limitation of gemifloxacin.
The review addressed a well-defined question in terms of study design, participants, interventions and relevant outcomes. Relevant databases were searched for studies published in any language. Only a limited search was made for unpublished studies, so some relevant studies may have been missed. There appeared to be no evidence for publication bias. Study quality was assessed using suitable criteria and studies were mostly of adequate quality. Efforts were made to reduce error and bias throughout the review process. Relevant study details were reported. The synthesis was appropriate but insufficient detail was provided to explain the results provided for clinically evaluable populations. In general the review process and study quality were adequate.

Combining results for different types of comparison antibiotics was problematic; however, there was not a high level of heterogeneity for most outcomes. For some outcomes there was no evidence of a difference between gemifloxacin and the comparison antibiotics but wide confidence intervals meant that they may not necessarily be equivalent as stated by the authors. Other analyses were difficult to interpret because of the small numbers of trials and events included. The authors’ conclusions generally reflect the evidence presented but these uncertainties suggest that they should be regarded as provisional.

Implications of the review for practice and research

Practice: The authors noted that gemifloxacin was more convenient than β-lactams and other quinolones as it was a short once-daily oral course. Due to oral administration, gemifloxacin may not be suitable for severely ill patients who require intravenous treatment. Quinolones have better penetration to lung tissue than β-lactams. The risk of rash should be considered when using gemifloxacin especially in younger women (under 40 years).

Research: The authors did not specifically report any implications for research but implied that they would recommend studies with longer term follow-up (more than six weeks).

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