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Title
Quinolones versus macrolides in the treatment of legionellosis: a systematic review and meta-analysis

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Keywords
Legionnaires- disease; Antimicrobial; Efficacy
Abstract

Background

Legionellosis is a life-threatening disease. The clinical superiority of quinolones or macrolides for treating patients with legionellosis has not been established.

Methods

We performed a systematic review and meta-analysis of studies reporting data for comparison of quinolones versus macrolides in the treatment of proven legionellosis published from 01/01/1985 to 31/01/2013. We collected baseline aggregate patient characteristics. Studied outcomes included mortality, clinical cure, time to apyrexia, length of hospital-stay and occurrence of complication in each treatment group. Treatment effect was assessed using a Mantel-Haenszel random effects model.

Results

Among 1005 abstracts reviewed, 12 studies were selected (n=879 patients). No randomized controlled trial (RCT) was available. Mean age was 58.3 years, 27.7% were women and Fine score was ≥4 in 35.8%. Among 253 patients with quinolone monotherapy, 10 died (4.0%). Among 211 patients with macrolide monotherapy, 23 died (10.9%). The pooled odds ratio of death when treated by a quinolone versus macrolide was 0.5 (95%CI=[0.2 – 1.3], n=8 studies, 464 patients). Length of stay was significantly lower in the quinolone monotherapy group. The difference was 3.0 days (95%CI=[0.7 – 5.3], p=0.001, n=3 studies, 263 patients). Both tests for heterogeneity were not significant ($I^2=0\%$ for both, p=1). Other studied outcomes were not significantly different among treatment groups.

Conclusion

Few clinical data on legionellosis treatment are available. This first meta-analysis showed a trend toward a lower mortality rate and a significant decrease in length of hospital-stay in patients receiving quinolone. These results must be confirmed by a randomized clinical trial.
**Introduction**

*Legionella pneumophila* is the most common intracellular bacteria responsible for severe pneumonia. Its incidence was estimated to 1.2 per 100 000 inhabitants in 2010. Risk factors include a male gender, a smoking habit, a history of chronic lung disease or immunosuppression, as well as travel and stay in large buildings, including hotels and hospitals. Prognosis factors include appropriateness and timing of initial antimicrobial therapy.

Legionellosis mostly presents as a mild-to-moderate disease. Severe systemic cases have been reported. The overall mortality has been estimated to 12%, and to 15-20% in hospitalized patients. Mortality seems higher in nosocomial cases (15-40% versus 10-20% in community-acquired cases). As a result, when initiating an empiric antimicrobial therapy for a severe pneumonia, current guidelines recommend to perform urinary diagnostic tests and to initiate a treatment for both *Streptococcus pneumoniae*, the most frequent bacteria involved in severe pneumonia, and *Legionella spp.*

Although erythromycin was the recommended treatment since the first reported outbreak of legionellosis, other agents have been developed. Recommended antimicrobials include quinolones and new macrolides. These recommendations are based on scarce data from *in vitro* and animal studies. Few data are available in humans and none allowed for a definitive conclusion. Consequently, the debate on which antimicrobial should be used in patients with legionellosis and/or to target *Legionella spp.* in patients with pneumonia is still ongoing.

No randomized clinical trial (RCT) has been performed for efficacy comparison. We performed a systematic review and meta-analysis to compare the clinical efficacy of a monotherapy of quinolone or macrolide in the treatment of legionellosis.

**Material and methods**

**Data sources**
Using Cochrane methodology, we conducted a systematic search of the literature. PubMed, Embase and the Cochrane Central Register of Controlled Trials databases were searched from 01/01/1985 to 01/31/2013. Search terms included: quinolone, fluoroquinolone, ofloxacin, ciprofloxacin, pefloxacin, trovafloxacin, levofloxacin, moxifloxacin, gatifloxacin, clinafloxacin, enoxacin, grepafloxacin, parfloxacin, norfloxacin, cinoxacin, macrolide, azithromycin, clarithromycin, erythromycin, spiramycin, roxithromycin. We also included related MeSH terms and Emtree entries. Two queries were performed. The first one (‘legionellosis query’, Table S1 as an example) aimed to identify studies providing data in legionellosis. In this query, ‘legionella’, ‘ legionnaire’ and ‘legionellosis’ terms were added to those aforementioned. In the second query, all RCTs performed to compare antimicrobial efficacy in community-acquired pneumonia were searched (‘RCTs in pneumonia query’, Table S2 as an example). In this second query, the term ‘pneumonia’ was added.

We searched additional references among the following scientific conferences from 2000 to 2012: Interscience Conference on Antimicrobial Agents and Chemotherapy, European Congress of Clinical Microbiology and Infectious Diseases, Infectious Disease Society of America and American Thoracic Society. Search terms included: ‘legionella’, ‘legionnaire’ and ‘legionellosis’.

Study selection

Title and abstract were independently assessed for eligibility by two authors (CB and RL). Full text of eligible studies and congress abstracts were independently examined for final inclusion. The opinion of a third investigator (YY) was asked in case of disagreement.

Original studies providing data for comparison of the efficacy of quinolones and macrolides in legionellosis were included. In vitro and animal studies were excluded. Legionellosis
Data extraction

Data were extracted using a standardized form: patient population, number of participating centres, number of patients included, antimicrobial agents and doses used, clinical outcomes, severity assessed by the Fine score and adverse effects.

Outcomes

Primary outcome was mortality in each treatment group. Secondary outcomes included clinical cure, time to apyrexia, length of hospital stay, occurrence of complications defined by studies’ authors, need for mechanical ventilation and occurrence of adverse effects.

Risk of bias assessment

Risk of bias was assessed using the Newcastle-Ottawa scale. This 8-item scale is suggested by the Cochrane collaboration for risk of bias assessment of nonrandomized studies. However we also used this scale for included RCTs.

Statistical analysis

The analysis focused on patients treated by antimicrobial monotherapy. β-lactams were not considered as effective anti-Legionella antimicrobials. We estimated pooled odds ratios and their 95% confidence intervals (95%CIs) comparing between quinolones and macrolides the probability of occurrence of qualitative outcomes. We estimated mean differences for time to apyrexia and length of hospital stay. Estimates were determined using a Mantel-Haenszel random effects model. Statistical heterogeneity was assessed using the chi-square test for heterogeneity and the P statistic for measuring inconsistency. Analyses were performed using Review Manager v5.2 (Cochrane Collaboration, Oxford, United Kingdom).

Results

Identification of eligible studies
Databases queries identified 1005 articles and/or congress abstracts. Most were not eligible, and 96 full-text articles were retrieved and read for inclusion (Figure 1). Of those, 12 were finally included. All were original articles. Nine were observational cohort studies, of which six were retrospective. They were performed in Spain (n=4), in France (n=2), and Japan (n=2). One was international. The three remaining studies were RCTs conducted in patients with pneumonia. Two of them were performed in the USA, the third was international. Five of the 12 studies were conducted in a single centre.

Risk of bias

Overall risk of bias is represented in Figure S1. Representativeness of general population was satisfactory. Patients included in observational studies were all patients with a proven diagnosis of legionellosis presenting in participating centres. Patients included in RCTs were representative of immunocompetent patients with community-acquired pneumonia. Ascertainment of therapy was performed using medical records or specific forms. All outcomes were prespecified and assessed using medical records or form completion. Follow up was adequate and long enough to ensure their assessment.

With the exception that by Dournon et al., no observational study controlled for confounding. Dournon et al. matched quinolone-treated patients with erythromycin-treated patient for age, duration of Legionnaires’ disease, immune status and requirement of mechanical ventilation. Patients treated with quinolone who received co-treatment with rifampicin and/or erythromycin were excluded from their analysis. Two RCTs did not stratify the randomization, and the other one stratified randomization on centre.

Patient characteristics in included studies

Overall, 879 patients with legionellosis were included (10 to 292 patients per study). Mean age was 58.3 years, and 27.7% of patients were women (n=223/806). All patients were
hospitalized at baseline, 55.1% (n=411/746) had an underlying disease, 19.8% (n=89/449) had a chronic obstructive pulmonary disease, and 65.9% (n=270/410) had a smoking habit. Data on immunosuppression was available in only 2 studies. In those, 63.6% (n=14/22) and 75% (n=45/60) of patients were immunocompromised. The Fine score was ≥ 4 in 35.8% (n=213/595).

Overall, 71 of the 879 patients with legionellosis enrolled in included studies (8.1%) died during follow up.

687 patients with legionellosis were treated with a quinolone (n=377, 54.9%) or macrolide (n=310, 45.1%) monotherapy (Table 1). In studies providing the information, 26.0% (n=47/181) of quinolone-treated patients had a Fine score ≥ 4, versus 32.7% (n=36/110) of patients in the macrolide group.

Outcomes

Mortality was reported in 8 studies (Figure 2A). Overall mortality occurred in 10.9% of patients treated with a macrolide (n=23/211) versus 4.0% of patients treated with a quinolone (n=10/253). The combined odds ratio of death when treated with quinolones versus macrolides was 0.5 [95%CI, 0.2; 1.3].

Clinical cure was evaluated in 4 studies. It was defined as resolution of signs and symptoms of pneumonia at the test-of-cure visit, performed depending on studies between day 1 and day 21 after the end of antimicrobial therapy. One study did not provide clinical cure definition. Clinical cure was observed in 100% of patients in 2 studies, which could not be used for computations. In the 2 other studies, the pooled odds ratio of clinical cure for treatment with a quinolone versus a macrolide was 2.3 [95%CI, 0.3; 16.9] (Figure 2B).

One study provided data for analysis of time to apyrexia. The time to apyrexia was shorter with quinolones than with macrolides, but the difference was not significant (mean difference, -4.8 hours [95%CI, -22.1; 12.5], Figure 2C).
Three studies were available for the comparison of length of hospital-stay (Figure 2D).\textsuperscript{23, 27, 28} One of them showed a significant reduction of the length of hospital-stay with quinolones \textit{versus} macrolides (-2.8, 95\%CI, -5.4; -0.2).\textsuperscript{23} We found an overall significant mean reduction of 3.0 days with quinolones \textit{versus} macrolides (95\%CI, -5.3; -0.7). Test for heterogeneity was not significant (I\textsuperscript{2}=0\%, p=0.9).

Two studies were included in the analysis of complications (Figure 2E).\textsuperscript{23, 25} These studies defined complicated legionellosis either as the apparition of pleural effusion, empyema, mechanical ventilation or septic shock;\textsuperscript{25} or renal failure, pleural effusion or admission to ICU.\textsuperscript{23} The combined odds ratio of complications when treated with quinolones \textit{versus} macrolides, was 0.5 [95\%CI, 0.1; 1.6]).

\textbf{Adverse effects}

In the only study providing data on adverse events,\textsuperscript{23} the three main reported events were gastrointestinal events (5 – 7\%), liver abnormalities (2 – 3\%) and phlebitis, which occurred more frequently in patients receiving clarithromycin than in those under levofloxacin therapy (p<0.01).

\textbf{Discussion}

This is the first systematic review and meta-analysis of the effectiveness of quinolones \textit{versus} macrolides in the treatment of legionellosis. We found that despite a small number of studies addressing this issue in clinical settings – and a small number of patients in each study – quinolones seem to have a higher effectiveness than macrolides. Quinolone therapy was significantly associated with a shorter length of hospital-stay, and we observed a trend toward a reduced mortality, a higher clinical cure, a lower time to apyrexia, and a lower rate of complications in patients receiving a quinolone.

Our analysis is unique. Published reviews on this topic did not use a systematic methodology for studies inclusion and results analysis.\textsuperscript{29, 30} In the absence of RCTs, the type
of analysis we conducted is the most accurate way to compare quinolones and macrolides effectiveness in patients with legionellosis and to improve management of this disease.

This question has been investigated in experimental models. In all but one of the 19 intracellular models reviewed by Pedro-Botet and Yu, quinolones had a higher activity on *Legionella pneumophila* than macrolides.\(^9\) Levofloxacin was the most effective quinolone and azithromycin the most effective macrolide. In animal models of *Legionella pneumophila* infection, treatment with quinolones resulted in an increased survival.\(^9\) However, these experimental results may not be generalisable to humans.

Despite a non-significant difference, results for all studied outcomes favoured quinolones. The absence of significance in these comparisons may be related to a lack of statistical power. However, none of the included studies attempted to control for confounding. Patients treated with macrolides had higher severity of disease. This might favour quinolones. Moreover, the macrolide agent used was mostly erythromycin, which is not the most effective macrolide agent as observed in *in vitro* studies.\(^9\) It was the only macrolide used in the study performed by Dournon *et al.*,\(^18\) in which the number of deaths in the macrolide group accounted for 40% of overall deaths observed in our review, and with a mortality rate of 50% in this group.

This study has some other limitations. First, statistical methodology is limited by the observational design of most included studies. RCTs were not designed for a proper analysis in legionellosis. We used random effects modelling to limit inherent bias. Moreover, our results are strengthened by the absence of heterogeneity. Second, a small number of studies were included. Legionellosis is a rare disease. The systematic strategy used for inclusion aimed to minimize misidentifications and to limit publication bias. However, reporting bias is a recurrent problem in systematic reviews and unpublished work could not be retrieved by our search strategy. Third, we were not able to perform subgroup analysis and/or to adjust on
disease severity or prognosis factors. Finally, we could not perform a face-to-face comparison of individual quinolones and macrolides as individual data were not available.

In light of our results, should we prefer quinolones or macrolides when treating a patient with a proven *Legionella* pneumonia? Our analysis does not provide a high level of evidence for conclusion. When answering this thorny question, risks associated with the administration of these antimicrobials should be considered. Quinolones are generally well-tolerated drugs; serious adverse events are rare. There is a rare risk of cardiac toxicity with macrolides, but azithromycin is generally considered to be free of serious adverse effects. Both quinolones and macrolides have been associated with an increased risk of developing a *Clostridium difficile* infection, with a higher risk for quinolones. The emergence of bacterial resistance in the digestive microbiota has been documented with quinolones, but such consideration should not restrain their use when treating a potentially fatal infection.

We believe that quinolones might be preferred for proven legionellosis, especially in patients with severe legionellosis. Empirical antimicrobial therapy for patients with severe pneumonia might benefit of a combination of a β-lactam and a quinolone, when a *Legionella* infection is suspected. However, in patients with mild pneumonia from uncertain origin, the potential negative impact of quinolones on the digestive microbiota should be balanced with their possible higher efficacy than macrolides.

This analysis should be confirmed by an international trial. With almost 5000 cases reported in Europe by the European Legionnaires’ Disease Surveillance Network in 2011, such trial would bring a definitive conclusion to the recurrent question of antimicrobial selection in *Legionella* pneumonia.

**Funding**

This study was supported by internal funding.

**Meetings**
This work has been presented in the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy, held in Denver, USA, from 10 to 13 September 2013 (Poster L-1319).

This work has been presented in the 15th Journées Nationales d'Infectiologie, held in Bordeaux, France, from 11 to 13 June 2014 (Poster I-07).

**Transparency declaration**

Pr. Yazdanpanah has received travel grants, honoraria for presentation at workshops, and consultancy honoraria from Bristol-Myers Squibb, Gilead, Merck, Pfizer, Roche, Tibotec, and ViiV Healthcare.

Other authors reported no conflict of interest.
References


Figure 1. Flowchart of studies inclusion. RCTs, randomized controlled trials.

- 808 records identified through the ' legionellosis' query
- 242 records identified through the 'RCTs in pneumonia' query

1005 records screened after duplicates removed

909 records excluded:
- review, n=480
- not a comparative study, n=202
- not a clinical study, n=175
- not a study in legionellosis or pneumonia, n=102

96 full-text articles assessed for eligibility

84 full-text articles excluded:
- no comparison in legionellosis, n=49
- no data for comparison of quinolones and macrolides, n=32
- not a original study, n=2
- congress abstract published as article, n=1

12 studies included in analysis
Figure 2. Comparison of quinolones and macrolides effectiveness in *Legionella* pneumonia.

A, analysis of mortality; B, analysis of clinical cure; C, analysis of the time to apyrexia (hours); D, analysis of length of hospital stay (days); E, analysis of the occurrence of complications.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Quinolones Events</th>
<th>Total</th>
<th>Macrolides Events</th>
<th>Total</th>
<th>Weight</th>
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<td>2</td>
<td>7</td>
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<td>0.40 [0.06, 2.57]</td>
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<td>2</td>
<td>2</td>
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<td>143</td>
<td>0</td>
<td>65</td>
<td>7.0%</td>
<td>1.38 [0.06, 34.30]</td>
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<tr>
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Total events 10 23

Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%

Test for overall effect: Z = 1.42 (P = 0.16)

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<th>Macrolides Events</th>
<th>Total</th>
<th>Weight</th>
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<td>5</td>
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<td>143</td>
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<td>65</td>
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<tr>
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<td>2.36 [0.33, 16.92]</td>
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Total events 146 70

Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%

Test for overall effect: Z = 0.85 (P = 0.39)

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<td>0.54 [0.05, 0.95]</td>
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Heterogeneity: Not applicable

Test for overall effect: Z = 0.54 (P = 0.59)

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<td>Nakamura 2009</td>
<td>29.6</td>
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<td>12</td>
<td>32.3</td>
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<td>0.01 [0.00, 0.02]</td>
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Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 2 (P = 0.94); I² = 0%

Test for overall effect: Z = 2.57 (P = 0.01)

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<td>Total (95% CI)</td>
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Total events 10 21

Heterogeneity: Tau² = 0.33; Chi² = 1.42, df = 1 (P = 0.23); I² = 29%

Test for overall effect: Z = 1.25 (P = 0.21)
Table 1. Main characteristics and outcomes of the studies included in the analysis according to monotherapy treatment group. AZM, azithromycin; CIP, ciprofloxacin; CLR, clarithromycin; ERY, erythromycin; LVX, levofloxacin; RXM, roxithromycin; M, macrolide monotherapy; OFX, ofloxacin; PEF, pefloxacin; PAZ, pazufloxacin; Q, quinolone monotherapy; SD, standard deviation; SPX, sparfloxacin; TVA, trovafloxacin. Missing data of presented variables were not available in the corresponding studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Enrolment period</th>
<th>Number of patients with legionellosis</th>
<th>Agent(s) used (n)</th>
<th>Mean age (years)</th>
<th>Proportion of women (%)</th>
<th>Underlying disease, n (%)</th>
<th>Fine score ≥4, n (%)</th>
<th>Overall mortality, n (%)</th>
<th>Mean time to apyrexia, hours (SD)</th>
<th>Mean hospital stay, days (SD)</th>
<th>Secondary complication, n (%)</th>
<th>Clinical cure, n (%)</th>
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<td>Dournon 1990</td>
<td>1980-1988</td>
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