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Respiratory fluoroquinolones for the treatment of community-acquired pneumonia: a meta-analysis of randomized controlled trials

Konstantinos Z. Vardakas MD, Ilias I. Siempos MD, Alexandros Grammatikos MD, Zoe Athanassa MD, Ioanna P. Korbila MD, Matthew E. Falagas MD DSc

∞∞ See related commentary by Low, page 1245

Abstract

Background: We investigated whether the use of respiratory fluoroquinolones was associated with better clinical outcomes compared with the use of macrolides and β-lactams among adults with pneumonia.

Methods: We searched PubMed, Current Contents, Scopus, EMBASE, ClinicalTrials.gov and Cochrane with no language restrictions. Two reviewers independently extracted data from published trials that compared fluoroquinolones (levofloxacin, moxifloxacin, gemifloxacin) with macrolides or β-lactams or both. A meta-analysis was performed with the clinical outcomes of mortality, treatment success and adverse outcomes.

Results: We included 23 trials in our meta-analysis. There was no difference in mortality among patients who received fluoroquinolones or the comparator antibiotics (OR 0.85, 95% CI 0.65–1.12). Pneumonia resolved in more patients who received fluoroquinolones compared with the comparator antibiotics for the included outcomes in the intention-to-treat population (OR 1.17, 95% CI 1.00–1.36), clinically evaluable population (OR 1.26, 95% CI 1.06–1.50) and the microbiologically assessed population (OR 1.67, 95% CI 1.28–2.20). Fluoroquinolones were more effective than a combination of β-lactam and macrolide (OR 1.39, 95% CI 1.02–1.90). They were also more effective for patients with severe pneumonia (OR 1.84, 95% CI 1.02–3.29), those who required admission to hospital (OR = 1.30, 95% CI 1.04–1.61) and those who required intravenous therapy (OR = 1.44, 15% CI 1.13–1.85). Fluoroquinolones were more effective than β-lactam and macrolide in open-label trials (OR = 1.35, 95% CI 1.08–1.69) but not in blinded randomized controlled trials (OR = 1.13, 95% CI 0.85–1.50).

Interpretation: Fluoroquinolones were associated with higher success of treatment for severe forms of pneumonia; however, a benefit in mortality was not evident. A randomized controlled trial that includes patients with severe pneumonia with or without bacteremia is needed.

Une version française de ce résumé est disponible à l'adresse www.cmaj.ca/cgi/content/full/179/12/1269/DC1

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Community-acquired pneumonia is among the leading reasons for hospital admission[1] and resource consumption.[2,3] It is the most frequent cause of community-acquired infections among patients admitted to intensive care units.[4] In addition, it is among the leading causes of death worldwide.

Physicians must choose an optimal therapeutic regimen that eliminates the infection effectively, minimizes the risk of developing drug resistance and does not compromise the safety of the patient. The combination of β-lactam and macrolide covers the most common possible pathogens involved in the pathogenesis of pneumonia.[5] More recently, fluoroquinolones with enhanced activity against *Streptococcus pneumoniae* were introduced in clinical practice. The favourable pharmacokinetic profile of fluoroquinolones allows for once daily administration, often eliminating the need for parenteral treatment. Furthermore, initial treatment with fluoroquinolones was among the predictors of lower treatment failure among patients with pneumonia.[6]

In 2007, the Infectious Diseases Society of America and the American Thoracic Society released new guidelines for the management of care for adult patients with community-acquired pneumonia.[7] In these guidelines, levofloxacin, gemifloxacin and moxifloxacin were reported to be equally effective as the combination of β-lactam and macrolide, and were proposed to be the preferred treatment option for patients who require admission to hospital, as well as for patients with comorbidity who receive treatment as outpatients. In addition to being safe, these fluoroquinolones are more effective against the most common types of bacteria responsible for the development of community-acquired pneumonia.[7] For example, *S. pneumoniae* strains are not fully susceptible to ciprofloxacin. On the other hand, trovafloxacin, clinafloxacin, gatifloxacin and other quinolones are not used because of safety concerns or because they are not widely available. The trials that compared fluoroquinolones with other antibiotics regimens for the treatment of pneumonia were designed on

From the Alfa Institute of Biomedical Sciences (Vardakas, Siempos, Grammatikos, Athanassa, Korbila, Falagas), Athens, Greece; and Tufts University School of Medicine (Falagas), Boston, USA

the basis of noninferiority (i.e., an antibiotic is equally effective to a comparator), and several were conducted in order to receive approval from the relevant agencies.

We sought to examine whether the use of fluoroquinolones was associated with more advantages or disadvantages than the use of macrolides or β-lactams in terms of mortality, resolution of pneumonia and adverse effects.

Methods

Search strategy

We searched PubMed (1980–2008), Current Contents, Scopus, EMBASE, ClinicalTrials.gov and the Cochrane Central Register of randomized controlled trials using the search terms "community-acquired pneumonia" and "fluoroquinolones," "levofloxacin," "moxifloxacin," "gemifloxacin," "macrolides" or "β-lactams." Whenever possible, the search was limited to randomized controlled trials. We reviewed the references from the relevant articles, which included review articles. We did not include abstracts from conferences because there is frequently considerable difference between data presented in conference abstracts and the subsequent peer-reviewed publications.[8,9]

Study selection

Two reviewers (I.I.S. and A.G.) independently searched the literature and examined the identified relevant trials for data on effectiveness and toxicity. We considered a trial to be eligible for inclusion in our primary analysis if it compared a fluoroquinolone proposed in the 2007 Infectious Diseases Society of America and the American Thoracic Society guidelines (levofloxacin, gemifloxacin, moxifloxacin) to combination therapy consisting of macrolide and β-lactam, or to monotherapy (macrolide, ketolide or β-lactam alone) for the treatment of pneumonia. We excluded trials that compared fluoroquinolones other than those proposed in the guidelines. The inclusion of hospital inpatients was not a prerequisite for eligibility. Trials that included the use of additional antimicrobial agents (mainly those with effectiveness against multi-drug resistant bacteria) were included. We did not set any language restrictions.

Data extraction

Two reviewers (Z.A. and I.P.K.) independently extracted the relevant data. Any disagreement was resolved by consensus at meetings with all authors. The corresponding authors of the original trials were contacted if additional data were necessary. A quality review of each trial was performed to include details of randomization, generation of random numbers, double-blinding, information on withdrawals, and concealment of allocation. We awarded 1 point for the specification of each criterion to a maximum of 5 points. Trials that scored more than 2 points were considered high quality, and those that scored 2 or fewer points were considered low quality.[10]

Definitions of infections

We included trials that defined pneumonia according to the following criteria: a baseline chest radiograph that demonstrated new or progressive infiltrates, or consolidation with or without effusion, and 4 of the following signs and symptoms: cough, new or worsened purulent sputum production, rales or signs of pulmonary consolidation or both, dyspnea or hypoxemia or both, fever (≥ 38°C), respiratory rate greater than 20 breaths/min, systolic hypotension (< 90 mm Hg), heart rate greater than 120 beats/min; altered mental status, requirement for mechanical ventilation, leukocyte count 10 000 cells/mm^3 or greater with ≥ 15% immature neutrophils, or leukopenia (leukocyte count ≤ 4500 cells/mm^3). For the purpose of our meta-analysis, we considered the severity of pneumonia according to the definitions provided in the individual trials.

We defined bacteremic pneumonia as the presence of *S. pneumoniae* or another pathogen commonly implicated in the development of pneumonia in 1 or more blood samples, and a clinical profile compatible with a diagnosis of pneumonia.

Outcomes

Our primary outcome was all-cause mortality in the intention-to-treat population during the study period (e.g., during treatment and follow-up period). Patients who received at least 1 dose of a study medication were included in the intention-to-treat analysis. We also assessed mortality in subgroups of patients with severe pneumonia and bacteremia.

Treatment success ("cure" was defined as resolution of all symptoms and signs of infections; "improvement" was defined as resolution of 2 or more of the baseline symptoms or signs of infections) and adverse outcomes probably or possibly related to the study regimens were considered as secondary outcome measures. Treatment success was assessed in the intention-to-treat population and in the clinically evaluable population (patients who completed the course of treatment and for whom outcome could be assessed at the end of each trial). We also assessed treatment success separately for patients with severe, moderate and mild pneumonia, bacteremic pneumonia, patients who received initial intravenous or oral therapy, those who required hospital admission, those who received levofloxacin, moxifloxacin or gemifloxacin, those who received monotherapy or combination therapy with β-lactam and macrolide, and patients in the microbiologically evaluable population (patients in the clinically evaluable population with microbiologically confirmed pneumonia) at the test-of-cure visit (i.e., when the clinical outcome was assessed) as defined in each trial. We also assessed adverse outcomes probably or possibly related to the study drugs and the duration of stay in hospital.

We performed sensitivity analyses to assess the robustness of the trial findings according to 2 different aspects of the trials methodology: high score on the modified Jadad scale (> 2) and use of double blinding. We also performed additional analyses based on whether the study was industry or nonindustry funded.

Data analysis and statistical methods

We assessed heterogeneity between trials using the χ^2 and I^2 tests. In the analysis of heterogeneity, we considered a p value lower than 0.10 to be statistically significant. We assessed

publication bias using the funnel plot method and Egger's test.[11] We calculated pooled odds ratios (OR) and 95% confidence intervals (CI) for all primary and secondary outcomes using both the Mantel–Haenszel fixed effects[12] and the DerSimonian–Laird random-effects models.[13] For all analyses, the results from the fixed-effects model are presented only when there was no heterogeneity between trials; otherwise, the results from the random-effects model are presented.

Results

Included trials

We identified a total of 1365 articles that reported on pneumonia treated with fluoroquinolones, β-lactams and macrolides. Of these, 1086 were excluded because they were not randomized controlled trials. An additional 256 trials were excluded because of reasons shown in Figure 1. Thus, we included 23 trials (which included 7885 patients) in our meta-analyses.[14–36] The 2 reviewers had initial agreement on 943/1058 (89%) entries for methodology and outcomes (kappa statistic = 0.78).

We contacted the corresponding authors of 19 studies. Of these, 2 authors provided the requested data; 5 additional authors reported that the requested data were not available. We did not find publication bias in the performed analyses. Appendix 1 (available online at www.cmaj.ca/cgi/content/full/179/12/1269/DC2) presents the outcomes of the trials included in the meta-analysis.

The main characteristics of the analyzed trials are shown in Appendix 2 (available at www.cmaj.ca/cgi/content/full/179/12/1269/DC2) and Appendix 3 (available at www.cmaj.ca/cgi/content/full/179/12/1269/DC2). Of the included trials, 8 trials included only patients with severe or moderate-to-severe pneumonia.[16,18,19,21,22,28,30,36] Six additional trials enrolled patients with severe pneumonia;[17,26,27,29,33,34] however, the majority of enrolled patients had mild to moderate pneumonia. The guidelines of the American Thoracic Society[37] and Pneumonia Severity Index score class IV and V[38] were mainly used for assessment of severe pneumonia. Criteria for hospital admission varied between trials, and the need for initial intravenous treatment was the main reason for admission to hospital. Five trials included outpatients.[15,20,23,24,33] Both intravenous and oral administration were used depending on the severity of pneumonia and the ability of patients to receive medications orally.

For all included trials, we excluded patients from the effectiveness analysis if they had received any antibiotics for treatment of pneumonia in the 24–48 hours before enrollment, unless the isolated pathogen was resistant to these antibiotics or treatment had failed (according to the opinion of the investigators). No data were available from the trials about the management of pneumonia caused by microorganisms that may have been resistant to the study medication.

Details about drug resistance patterns were reported in 13 trials.[14–18,20,21,26,27,29–32] Isolates recovered from all patients enrolled in the studies were tested for resistance against the study antibiotics and for penicillin resistance. Only one *S. aureus* isolate resistant to levofloxacin was found in these 13 studies. *S. pneumoniae* strains resistant to the comparator antibiotics were more commonly found (1%–33%). Resistance was more prominent among macrolides (8%–33% for all isolates) than among β-lactams (0%–11.5% for all isolates). Intermediate resistance to penicillin was a more common finding (8%–29% for all isolates).

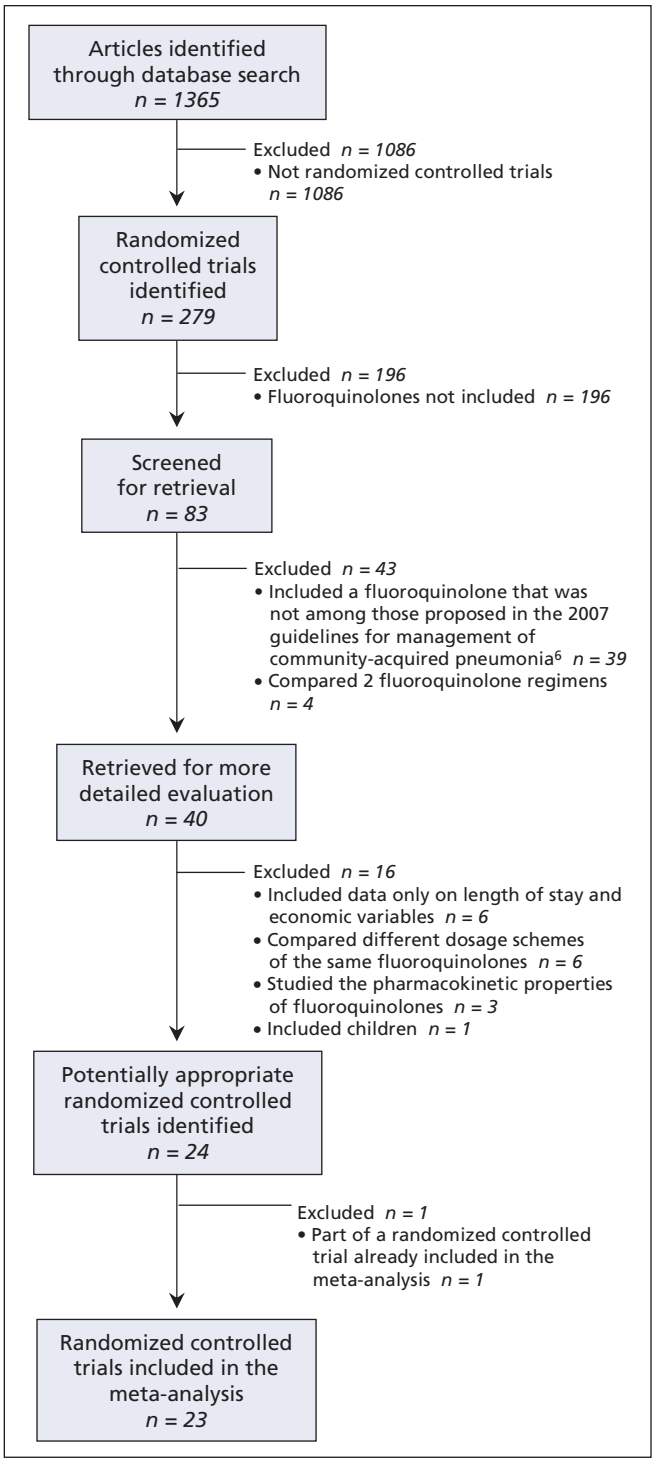

Figure 1: Retrieval and selection of randomized controlled trials for inclusion in the meta-analysis of the effectiveness of fluoroquinolones for the treatment of pneumonia.

Mortality

Data about mortality in the intention-to-treat population were provided in 18 trials[14–19,21,22,24,26,27,29–34,36] and ranged from 0% to 7% (mean 2.7%) in the fluoroquinolone groups and from 0.5% to 8% (mean 3.4%) in the comparator groups. Mortality rates were not different between the 2 groups of patients (Figure 2, OR 0.85, 95% CI 0.65–1.12). Data about mortality among patients with severe pneumonia were only available for 1 trial,[16] and data about mortality of patients with bacteremic pneumonia were available for 2 trials;[16,31] thus, we did not perform a combined analysis. Mortality rates were not different when we excluded trials that included outpatients (OR 0.92, 95% CI 0.68–1.24).

Treatment success

Data about treatment success in the intention-to-treat population were available for 15 trials.[14,15,19–21,26–28,31–36] Overall, treatment with fluoroquinolones was successful for 84.2% of patients. Treatment with comparator antibiotics was successful for 82.2% of patients. Pneumonia was cured or improved for significantly more patients in the fluoroquinolones group than in the comparison group (Figure 3, OR 1.17, 95% CI 1.00–1.36).

All trials provided data about treatment success in the clinically evaluable population.[14–36] The effectiveness of both antibiotic regimens was high (fluoroquinolones 91.9%, comparator antibiotics 89.7%). However, our meta-analysis showed that fluoroquinolones were more effective than the comparators antibiotics for the treatment of pneumonia (OR 1.26, 95% CI 1.06–1.50). Fluoroquinolones were also more effective than combination therapy (OR 1.39, 95% CI 1.02–1.90). However, there was no difference in treatment success when fluoroquinolones were compared with β-lactam or macrolide monotherapy (OR 1.19, 95% CI 0.93–1.50). In the analysis that included only trials not funded by pharmaceutical companies, fluoroquinolones were more effective than the comparator antibiotics (OR 1.86, 95% CI 1.26–2.75) (Appendix 4: available at www.cmaj.ca/cgi/content/full/179/12/1269/DC2).[18,22,25,27,31,35] However, they were not more effective in the analysis that included trials funded by pharmaceutical companies (OR 1.13, 95% CI 0.93–1.38).[14–17,19–21,23,24,26,28–30,32–34,36]

Twelve trials included patients with severe pneumonia; of these, 7 reported data from this population.[16,19,26,27,29,33,34] In this subgroup, fluoroquinolones were more effective than the comparator antibiotics (OR 1.84, 95% CI 1.02–3.29). Data about patients with severe pneumonia who received combination therapy or monotherapy were not provided separately. However, fluoroquinolones were not more effective than comparator antibiotics for treatment of mild to moderate pneumonia (OR 1.22, 95% CI 0.98–1.51)[14,15,17,18,20,22–29,31] and moderate-to-severe pneumonia (OR 1.43, 95% CI 1.01–2.04).[16,18,19,21,27,28,30,33,36]

In 11 trials, fluoroquinolones were administered orally.[14–17,20,23,24,27,29,31–33] In 3 of these trials, the comparator antibiotics were initially administered intravenously.[16,17,29] In this subgroup of 11 trials, fluoroquinolones were not more effect-

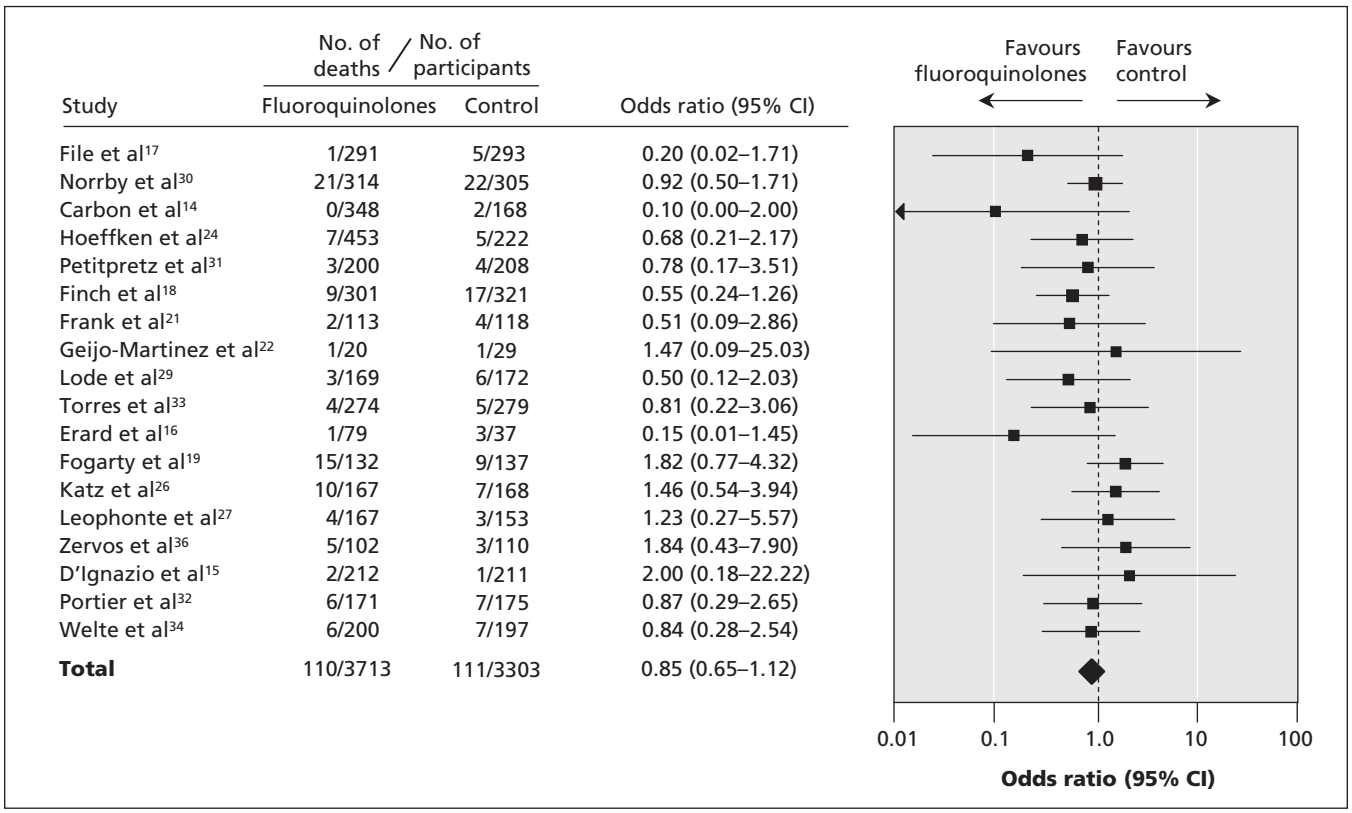

Figure 2: Effect of fluoroquinolones on mortality among patients with pneumonia in the intention-to-treat population. Test for heterogeneity: $\chi^2 = 14.25$, $p = 0.65$, $I^2 = 0\%$. Test for overall effect: z = 1.12, $p = 0.26$. Note: CI = confidence interval.

ive than comparator antibiotics (OR 1.10, 95% CI 0.85–1.41). In trials that used initial intravenous treatment for either antibiotic regimen, fluoroquinolones were more effective than comparator antibiotics (OR 1.44, 95% CI 1.13–1.85).[17–19,21,22,25,26,28,34–36] For trials that included outpatients, there was no benefit with fluoroquinolone treatment (OR 1.06, 95% CI 0.75–1.50).[15,20,23,24,33] Among patients in hospital, treatment success was significantly higher with use of fluoroqunilones than with comparator antibiotics (OR 1.30, 95% CI 1.04–1.61).[16,18,19,21,25–32,34–36]

When we examined the effectiveness of individual fluoroquinolones, we found no difference between levofloxacin and the comparator antibiotics (OR 1.28, 95% CI 0.97–1.67).[14–17,19,21–23,25,28,30,36] Similar findings were reported for moxifloxacin (OR 1.22, 95% CI 0.95–1.55). Levofloxacin was administered to outpatients in 3 trials,[14,15,23] and it was administered orally in 4 trials.[14–16,23] Moxifloxacin was administered to outpatients in 2 trials,[20,24] and it was administered orally in 5 trials.[20,24,31–33]

In the microbiologically evaluable population, fluoroquinolones were more effective than comparator antibiotics (OR 1.67, 95% CI 1.28–2.20).[14,15,17–24,26–32,35] For the subgroup of patients with pneumonia due to *S. pneumoniae,* there was no difference in effectiveness (OR 0.72, 95% CI 0.39–1.33).[15,17,19,27–29,31,32,35,36] Data about other possible pathogens, including *Hemophilus influenzae*, *S. aureus*, *Pseudomonas* spp and atypical pathogens, were not reported consistently. There was no difference in effectiveness among patients with bacteremic pneumonia (OR 0.84, 95% CI 0.37–1.89)[16,18,20,21,26,27,29,31,32,36] or bacteremic pneumonia due to *S. pneumoniae* (OR 1.30, 95% CI 0.43–3.95).[17–19,21,26,27,29,32,36]

Duration of hospital stay

Data about the duration of stay in hospital were available for 9 trials.[16,18,22,28–30,33,34,36] Because duration was not uniformly presented, we could not perform a pooled analysis. In total, 5 trials[16,29,30,33,34] provided the median, and 4 trials[18,22,28,36] provided the mean duration of hospital stay. Patients who received fluoroquinolones stayed in hospital 1–2 days less than those who received comparator antibiotics in the trials that reported the median length of stay. However, there was no difference in the length of stay in trials that reported the mean length of stay.

Quality assessment and sensitivity analyses

The mean quality score of the included trials was 2.6 (range 1–5). The quality of 11 trials was high.[14,15,19–21, 24,26–28,30,33] The quality of the other 12 studies was low.[16–18,22,23,25,29,31,32,34–36] There was no difference in the effectiveness of fluoroquinolones and comparator antibiotics in the trials that were of high quality (OR 1.22, 95% CI 0.95–1.57). In the analysis of low-quality trials, fluoroquinolones were associated with significantly improved treatment success (OR 1.30, 95% CI 1.01–1.67). There was no difference between the antibiotic regimens in sensitivity analyses that included only double-blinded trials (OR 1.13, 95% CI 0.85–1.50).[14,15,20,23,24,27,31,33] However, there was a significant difference in favour of fluoroquinolones when only open-label trials were included (OR 1.35, 95% CI 1.08–1.69).[13–19,21,22,25,26,28–30,32,34–36]

Study	No. of treatment successes / No. of participants: Fluoroquinolones	Control	Odds ratio (95% CI)
Norrby et al[30]	239/314	229/305	1.06 (0.73–1.53)
Carbon et al[14]	286/348	144/168	0.77 (0.46–1.28)
Fogarty et al[20]	219/235	221/238	1.05 (0.52–2.14)
Petitpretz et al[31]	173/200	171/208	1.39 (0.81–2.38)
Frank et al[21]	95/106	90/105	1.44 (0.63–3.30)
Torres et al[33]	218/233	229/244	0.95 (0.45–1.99)
Fogarty et al[19]	96/132	88/137	1.48 (0.88–2.49)
Katz et al[26]	93/111	93/116	1.28 (0.65–2.52)
Leophonte et al[27]	143/167	128/153	1.16 (0.63–2.14)
Zervos et al[36]	83/93	87/97	0.95 (0.38–2.41)
D'Ignazio et al[15]	189/212	180/211	1.42 (0.79–2.52)
Portier et al[32]	142/171	136/175	1.40 (0.82–2.40)
Welte et al[34]	150/200	140/197	1.22 (0.78–1.90)
Xu et al[35]	18/20	19/20	0.47 (0.04–5.69)
Lin et al[28]	18/26	17/24	0.93 (0.28–3.11)
Total	2162/2568	1972/2398	1.17 (1.00–1.36)

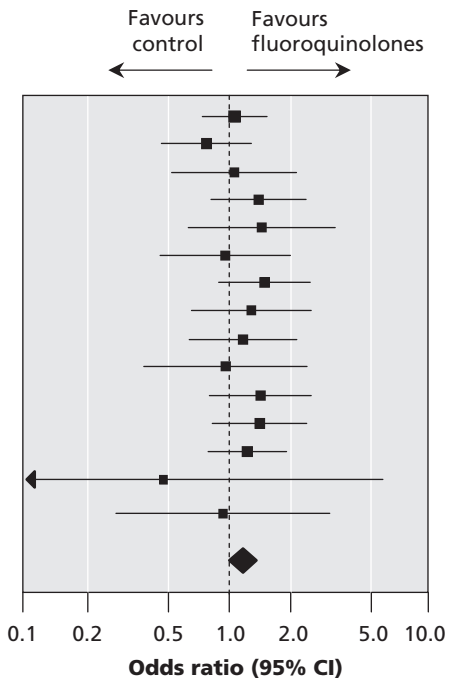

Figure 3: Odds ratios for treatment success with fluoroquinolone therapy among patients with pneumonia for the intention-to-treat and clinically evaluable populations. Test for heterogeneity: $\chi^2 = 6.49$, $p = 0.95$, $I^2 = 0\%$. Test for overall effect: z = 1.96, $p = 0.05$. Note: CI = confidence interval.

Adverse outcomes

All trials reported data about drug-related adverse outcomes in the intention-to-treat population. The majority of adverse outcomes were mild to moderately severe disturbances of the gastrointestinal tract. The most commonly studied adverse effects were photosensitivity, diarrhea, vomiting and nausea, liver function abnormalities, insomnia, headache and rash (Appendix 5: available at www.cmaj.ca/cgi/content/full/179/12/1269/DC2). Fluoroquinolones were associated with significant fewer adverse outcomes than comparator antibiotics (OR 0.86, 95% CI 0.78–0.96) (Figure 4). The percentage of patients who were withdrawn from the trials because of drug-related adverse outcomes was not different between groups (OR 0.85, 95% CI 0.69–1.06) and was mostly because of gastrointestinal disturbances. Thirteen trials reported data about recurrent infections.[14–17,20,24,28–32,34] There was no difference between fluoroquinolones and the compared antibiotics for this outcome (OR 0.98, 95% CI 0.59–1.63).

Interpretation

We found no differences in mortality between patients with community-acquired pneumonia who received fluoroquinolones and those who received a combination of β-lactam and macrolide or either antibiotic alone. In contrast, treatment success in the clinically evaluable and intention-to-treat populations was significantly higher among patients who received fluoroquinolones. This effect was more prominent among patients with severe pneumonia (9% absolute difference in treatment success). We also found that fluoroquinolones were more effective than the comparator antibiotics when administered in hospital or when initial treatment was administered intravenously. Trials that were not funded by industry showed a significantly higher treatment success among patients who received fluoroquinolones compared to the comparator antibiotics. Fluoroquinolones were also associated with fewer adverse outcomes. However, previous meta-analyses have reported that fluoroquinolones were associated with either more adverse outcomes compared with other antibiotics or no difference in toxicity was reported.[39–43]

The findings of our meta-analysis about overall treatment success were similar to the results of a meta-analysis published in 2002.[44] However, only 3 of the trials included in that meta-analysis studied the effectiveness of the fluoroquinolones proposed in the 2007 guidelines. In addition, the authors of the 2002 meta-analysis stated that data about mor-

Study	No. of adverse effects / No. of participants: Fluoroquinolones	Control	Odds ratio (95% CI)
File et al[17]	17/291	25/293	0.67 (0.35–1.26)
Norrby et al[30]	68/314	79/305	0.79 (0.55–1.15)
Carbon et al[14]	97/348	50/168	0.91 (0.61–1.37)
Fogarty et al[20]	84/235	83/238	1.04 (0.71–1.51)
Kalbermatter et al[25]	0/28	0/56	
Hoeffken et al[24]	166/453	81/222	1.01 (0.72–1.41)
Petitpretz et al[31]	56/200	42/208	1.54 (0.97–2.43)
Finch et al[18]	117/301	125/321	1.00 (0.72–1.38)
Frank et al[21]	6/113	11/118	0.55 (0.19–1.53)
Geijo-Martinez et al[22]	1/20	2/29	0.71 (0.06–8.41)
Gotfried et al[23]	29/143	41/156	0.71 (0.42–1.23)
Lode et al[29]	28/169	37/172	0.72 (0.42–1.25)
Torres et al[33]	55/274	86/279	0.56 (0.38–0.83)
Erard et al[16]	5/79	2/37	1.18 (0.22–6.40)
Fogarty et al[19]	98/132	96/137	1.23 (0.72–2.10)
Katz et al[26]	30/167	27/168	1.14 (0.65–2.02)
Leophonte et al[27]	31/167	35/153	0.77 (0.45–1.32)
Zervos et al[36]	36/102	49/110	0.68 (0.39–1.18)
D'Ignazio et al[15]	26/212	42/211	0.56 (0.33–0.96)
Portier et al[32]	42/171	50/175	0.81 (0.50–1.31)
Welte et al[34]	65/200	76/197	0.77 (0.51–1.16)
Xu et al[35]	2/20	1/20	2.11 (0.18–25.35)
Lin et al[28]	0/26	0/24	
Total	1059/4165	1040/3797	0.86 (0.78–0.96)

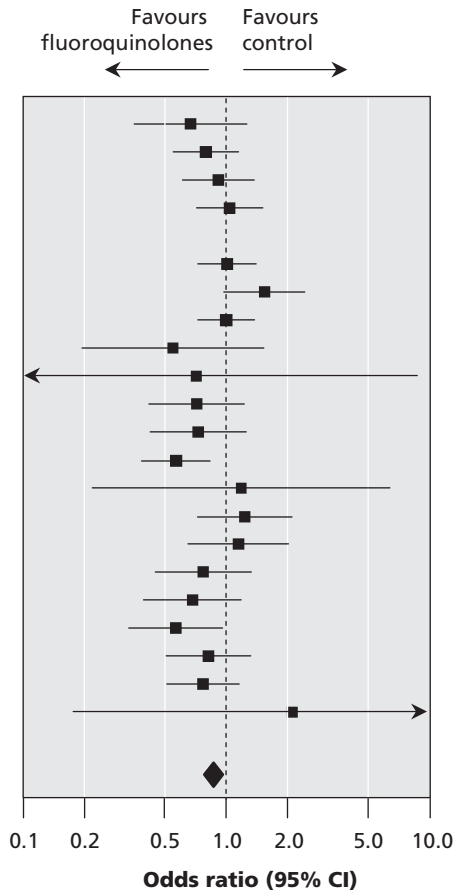

Figure 4: Odds ratios for adverse outcomes after fluoroquinolone therapy among patients with pneumonia in the intention-to-treat population. Test for heterogeneity: $\chi^2 = 22.81$, $p = 0.30$, $I^2 = 12.3\%$. Test for overall effect: $z = 2.72$, $p = 0.007$. Note: CI = confidence interval.

tality were not available. In addition, they did not differentiate between mild, moderate and severe forms of pneumonia, and they did not analyze data about bacteremic pneumonia.

The relatively low mortality reported in the individual trials supports the opinion that the patients enrolled in such trials are not at high risk for death.[45] In addition, most of the included trials did not provide data about mortality nor were they focused on severe pneumonia. This limited our ability to draw conclusions about the effectiveness of treatment in the most severely ill patients. Two non-randomized trials reported different conclusions; one favoured levofloxacin and one favoured a combination of β-lactam and macrolide.[46,47]

A possible explanation for the higher treatment success in the fluoroquinolone groups may be because there was zero baseline resistance of the isolated pathogens to fluoroquinolones compared to the higher levels of resistance found for β-lactams and especially macrolides. However, the trials included in our analysis mainly examined *S. pneumoniae* isolates. The impact of initially appropriate treatment with β-lactams for the treatment of pneumococcal pneumonia remains questionable.[48]

The Tracking Resistance in the United States Today (TRUST) study reported that although *S. pneumoniae* isolates were highly resistant to penicillin and azithromycin (15%–44% according to the age group of patients from whom the isolates were recovered), resistance to ceftriaxone and amoxicillin-clavulanate was lower (1%–10%) and was minimal for levofloxacin (0%–1.3%).[49,50] Other studies have reported similar findings.[51–54] In contrast, resistance among *H. influenzae* and *Morraxella catarrhalis* isolates was high for ampicillin (19%–98%) but minimal (0%–0.2%) for all other antibiotics.[49,50] However, resistance to fluoroquinolones may increase in the future, and this may have an impact on treatment outcomes.[55]

Administration of fluoroquinolones was associated with better treatment success among patients with severe pneumonia. The diversity in the definition of severe pneumonia among the individual trials and the use of the Pneumonia Severity Index score as a measure for severe pneumonia may limit this finding.[38] The use of the CURB–65 (confusion, urea, respiratory rate, blood pressure, age > 65) score may be more appropriate for the assessment of the severity of pneumonia.[56]

Fluoroquinolones were more effective than combination therapy but no differences were seen for monotherapy. This may be because the trials that used combination therapies enrolled mainly patients with more severe forms of pneumonia and, as noted above, fluoroquinolones were more effective than β-lactams or macrolides in patients with moderate to severe pneumonia. As well, severe pneumonia was an exclusion criterion in the majority of the trials that compared fluoroquinolones with monotherapy.

Patients with bacteremic pneumonia did not seem to benefit more from fluoroquinolones than from β-lactams or macrolides. We were not able to distinguish between severe and nonsevere bacteremic pneumonia in the included trials. Combination therapy that included macrolides but not fluoroquinolones was associated with lower mortality among patients with bacteremic pneumonia.[57–61] A review of pneumococcal bacteremic pneumonia treated with levofloxacin, which also included penicillin-resistant strains, found that 91% of these patients had a successful clinical response and mortality was lower than 1%.[62]

We found that orally administered fluoroquinolones were not more effective than orally administered β-lactams and macrolides. This is in contrast to the favourable pharmacokinetic profile of fluoroquinolones.[63,64] Oral administration was mainly used for patients with milder forms of pneumonia, for whom the success rate of treatment was expected to be higher. In these studies, levofloxacin dosage was suboptimal (500 mg instead of 750 mg or more as currently proposed), which may have influenced the results. In contrast, fluoroquinolones were more effective among patients who required admission to hospital or intravenous treatment, which indicates that fluoroquinolones might be the preferred antibiotic in this settings. However, the diversity of the criteria used for determining inpatient or intravenous treatment among the trials included in our meta-analysis may limit the generalizability of our findings.

Limitations

The major limitation of our meta-analysis is the relatively low quality of the included trials. Only 8 of the included trials were double-blinded. We performed a sensitivity analysis that included only trials that were of high quality or that were double-blinded. This analysis showed that fluoroquinolones were not more effective than comparator antibiotics for the treatment of pneumonia. Patients with milder forms of pneumonia were enrolled in these high-quality trials.

Another limitation was the inclusion of only trials that studied the fluoroquinolones included in the Infectious Diseases Society of America 2007 guidelines.[7] As a result, 39 trials were not included in the final analysis.

Finally, data on adjunctive therapies that may improve outcomes in patients with severe pneumonia (e.g., hydrocortisone, statins, angiotensin-converting-enzyme inhibitors) were not collected.[65]

We did not present data about the total duration of treatment or the duration of intravenous therapy. These outcomes are subject to the individual investigator's assessment of the need for additional antibiotic treatment because the optimal duration of treatment for pneumonia has not been thoroughly evaluated.[66] Second, in the studies that enrolled patients with mild to moderately severe pneumonia, the duration of treatment was predefined. Third, a recent meta-analysis showed that the duration of treatment is not associated with clinical outcomes among patients with mild to moderately severe pneumonia.[67]

Conclusion

The results of our meta-analysis suggest that fluoroquinolones may be considered for the treatment of community-acquired pneumonia. In particular, they should be considered for the more severe forms of pneumonia, as well as for patients who require admission to hospital and initial intravenous treatment. We found no differences in mortality between antibiotic regimens; however, data on mortality among patients

with severe pneumonia were not available in the trials included in the analyses. A well-designed randomized controlled trial including mainly patients with severe community-acquired pneumonia with or without bacteremia is needed. Finally, physicians are reminded that macrolides and β-lactams are also highly effective for the treatment of pneumonia, especially for the mild to moderate forms of the infection.

This article has been peer reviewed.

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Correspondence to: *Dr. Matthew E. Falagas, 9 Neapoleos St., 151 23 Marousi, Greece; fax 30-210-68 39 605; m.falagas@aibs.gr*

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