Treating acute exacerbations of chronic bronchitis and community-acquired pneumonia

How effective are respiratory fluoroquinolones?

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ABSTRACT

OBJECTIVE To provide family physicians with a review of evidence supporting fluoroquinolone therapy for defined patient populations with acute exacerbations of chronic bronchitis (AECB) and community-acquired pneumonia (CAP).

QUALITY OF EVIDENCE A MEDLINE search found surveillance studies, randomized controlled trials, outcome studies, and expert consensus opinion. Descriptions of patient populations for which fluoroquinolone therapy is recommended are based on level I and level III evidence.

MAIN MESSAGE A growing body of evidence supports fluoroquinolones as first-choice agents for treatment of AECB or CAP patients with comorbidity or a recent history of antibiotic use. Judicious and targeted therapy using fluoroquinolones among patients at risk of infections of the lower respiratory tract should contribute to improved clinical outcomes and broader health care savings.

CONCLUSION Current data show clinical utility and cost-effectiveness of fluoroquinolones in lower respiratory tract infections. The most recently issued AECB and CAP guidelines now recommend these antimicrobial agents as first-choice agents for specific patient populations.

RÉSUMÉ

OBJECTIF Présenter aux médecins de famille une revue des preuves appuyant l’emploi des fluoroquinolones pour traiter certaines catégories de patients présentant une exacerbation aiguë de bronchite chronique (EABC) ou une pneumonie extra-hospitalière (PEH).

QUALITÉ DES PREUVES Une recherche dans MEDLINE a permis d’identifier des études de suivi, des essais randomisés avec témoins, des études de résultats et des opinions provenant de consensus d’experts. La description des catégories de patients pour lesquels les fluoroquinolones sont recommandées repose sur des preuves de niveaux I et III.

PRINCIPAL MESSAGE Il y a de plus en plus de preuves indiquant que les fluoroquinolones constituent le premier choix pour traiter les EABC ou les PEH chez les patients présentant une comorbidité ou une histoire récente d’antibiothérapie. Une utilisation judicieuse et ciblée des fluoroquinolones chez les patients à risque d’une infection des voies respiratoires inférieures devrait contribuer à obtenir de meilleurs résultats cliniques tout en réduisant les coûts de traitement.

CONCLUSION Les données actuelles confirment l’utilité et la rentabilité des fluoroquinolones dans les infections des voies respiratoires inférieures. Les plus récentes directives de pratique concernant les EABC et les PEH recommandent ces agents antimicrobiens comme premier choix pour certaines populations de patients.

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lower respiratory tract infections, specifically acute exacerbations of chronic bronchitis (AECB) and community-acquired pneumonia (CAP), are substantial causes of patient morbidity and mortality. Cases of AECB account for approximately 1.5 million physician visits, and approximately 500,000 cases of CAP are diagnosed annually in Canada. While current Canadian guidelines do not advocate fluoroquinolones for first-line therapy in general, both the AECB and CAP guidelines recommend fluoroquinolones for patients with defined risk factors and for patients who have had recent antimicrobial therapy.

In addition to age and comorbidity, recent antibiotic use is now considered a risk factor because of increasing concern over bacterial resistance. Traditionally, ampicillin, tetracycline and doxycycline, broad-spectrum macrolides, second- or third-generation cephalosporin, or trimethoprim and sulfamethoxazole (TMP/SMX) are antimicrobials of choice for treating AECB and CAP. Growing resistance to these agents has raised concerns, however, about their continued effectiveness, particularly against multi-drug-resistant strains of *Streptococcus pneumoniae* and beta-lactamase-producing strains of *Haemophilus influenzae* and *Moraxella catarrhalis*.

This article reviews recent clinical and microbiological data supporting the effectiveness of respiratory fluoroquinolones in treatment of lower respiratory tract infections.

**Quality of evidence**

A MEDLINE search found articles reporting surveillance studies, randomized controlled trials, outcome studies, and expert consensus opinion. Relevant articles were retrieved using MeSH terms: acute exacerbations of chronic bronchitis (AECB) and community-acquired pneumonia (CAP), combined with fluoroquinolone. Abstracts from the Interscience Conference on Antimicrobial Agents and Chemotherapy and the European Congress of Clinical Microbiology and Infectious Diseases were also reviewed. Recommendations of patient populations appropriate for fluoroquinolone therapy are based on level I (well conducted randomized controlled clinical trials) and level III (expert opinion and case studies) evidence.

**Clinical efficacy of respiratory fluoroquinolones**

Tables 1 and 2 summarize the recently published data from randomized controlled clinical trials of respiratory fluoroquinolones in AECB and CAP. Overall efficacy of moxifloxacin, gatifloxacin, levofloxacin, and gemifloxacin in treating AECB typically compared the drugs with oral beta-lactams and macrolides. Similarly, studies of treatment outcomes in CAP have compared moxifloxacin, gatifloxacin, and levofloxacin with oral beta-lactam alone, ceftriaxone-macrolide combinations, or macrolide-beta-lactam combinations.

Because most of these trials were designed for registration purposes, equivalence between fluoroquinolone and comparator arms was expected in clinical and microbiological assessments. Nevertheless, statistically superior clinical and bacteriological outcomes have been observed among clinically characterized populations of fluoroquinolone-treated patients—particularly among patients with risk factors as defined in current treatment guidelines.

Overall, the data suggest that short courses of oral fluoroquinolone therapy are as effective as longer courses of comparators, including intravenous agents. Further, fluoroquinolone therapy is effective against commonly encountered resistant organisms. In AECB, use of moxifloxacin or gemifloxacin, in particular, resulted in less frequent exacerbation of disease and reduced requirement for antimicrobial therapy. Experts currently believe that eradication of *H influenzae* among high-risk patients (those who have poor forced expiratory volume in 1 second, more than 3 acute exacerbations yearly, heart disease, prolonged therapy with oral steroids, or supplemental oxygen use) is most likely responsible for prolonging the exacerbation-free interval.

High-risk CAP patients (hospitalized patients or outpatients with chronic obstructive pulmonary disease who receive steroid therapy, and patients who have used antibiotics in past 3 months) treated with fluoroquinolones reported faster resolution of symptoms and fewer adverse events with an overall reduction in health care costs. No significant differences in outcomes between treatment with fluoroquinolones versus treatment with macrolides were observed among low-risk CAP patients.

**Microbiological efficacy of newer respiratory fluoroquinolones**

Effective antimicrobial therapy for AECB requires an agent active against *H influenzae*, *M catarrhalis*, and *S pneumoniae* (and less commonly *Haemophilus parainfluenzae*, *Enterobacteriaceae* species, and *Pseudomonas aeruginosa*). The bacterial cause of CAP includes the
### Table 1. Respiratory fluoroquinolone efficacy in randomized controlled studies of acute exacerbations of chronic bronchitis

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DESIGN</th>
<th>MICROBIOLOGICALLY EVALUABLE PATIENTS N (n)</th>
<th>REGIMEN</th>
<th>DURATION (D)</th>
<th>CLINICAL OUTCOMES*</th>
<th>MICROBIOLOGY OUTCOMES‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilson et al 2004⁴</td>
<td>r, db, mc, mn</td>
<td>730 (150)</td>
<td>M: 400 mg oral od</td>
<td>5</td>
<td>M: 239/274 (87.2%) 95% CI (-3.0, 8.5) vs all combined comparators A: 83%; CL: 87.4%</td>
<td>M: 65/71 (91.5%) Combined A+CL+Cf 64/79 (81.0%)</td>
</tr>
<tr>
<td>Schaberg et al 2001⁷</td>
<td>r, db, mc, mn</td>
<td>575 (140)</td>
<td>M: 400 mg oral od AC: 625 mg oral tid</td>
<td>5</td>
<td>M: 251/261 (96.2%) 95% CI (0.4, 8.7)</td>
<td>M: 64/73 (87.7%) AC: 60/67 (89.6%) 95% CI (-12.5, 8.9)</td>
</tr>
<tr>
<td>DeAbate et al 2000⁸</td>
<td>r, db, mc</td>
<td>464 (237)</td>
<td>M: 400 mg oral od</td>
<td>5</td>
<td>M: 194/221 (87.8%)</td>
<td>M: 106/119 (89.1%) Az: 102/118 (86.4%) 95% CI (-6.1, 11.2)</td>
</tr>
<tr>
<td>Chodosh et al 2000⁹</td>
<td>r, db, mc</td>
<td>926 (420)</td>
<td>M: 400 mg oral od</td>
<td>5</td>
<td>M: 127/143 (88.8%)</td>
<td>M: 127/135 (94.1%) M: 138/145 (95.2%) CL: 115/127 (90.6%) 95% CI (-3.7, 10.5)</td>
</tr>
<tr>
<td>Wilson et al 1999⁵</td>
<td>r, db, mc, mn</td>
<td>649 (229)</td>
<td>M: 400 mg oral od</td>
<td>5</td>
<td>M: 287/322 (89.1%)</td>
<td>M: 89/115 (77.4%) CL: 71/114 (62.3%) 95% CI (3.6, 26.9)</td>
</tr>
<tr>
<td>Ball et al 2001¹⁵</td>
<td>r, db, dd, mc, mn</td>
<td>616 (112)</td>
<td>Ge: 320 mg oral od Tr: 200 mg oral od</td>
<td>5</td>
<td>Ge: 249/272 (91.5%) Tr: 241/275 (87.6%) 95% CI (-1.2, 9.0)</td>
<td>Ge: 46/59 (78.0%) Tr: 42/53 (79.2%) 95% CI (-9.4, 18.3)</td>
</tr>
<tr>
<td>Wilson et al 2001¹⁷</td>
<td>r, db, mc, mn</td>
<td>709 (97)</td>
<td>Ge: 320 mg oral od</td>
<td>5</td>
<td>Ge: 300/351 (85.5%)</td>
<td>Ge: 39/45 (86.7%) CL: 38/52 (73.1%) 95% CI (-2.0, 29.2)</td>
</tr>
<tr>
<td>Wilson et al 2003¹⁸</td>
<td>r, ol, db, mc, mn</td>
<td>272 (99)</td>
<td>Ge: 320 mg oral od Cx: 1 g iv od + Cl: 500 mg oral bid</td>
<td>5</td>
<td>Ge: 105/121 (86.8%) Cx: 91/112 (81.3%) 95% CI (-3.9, 14.9)</td>
<td>Ge: 30/48 (62.5%) Combined Cx+Cf: 31/51 (60.8%) 95% CI (-17.4, 20.9)</td>
</tr>
<tr>
<td>Gotfried et al 2001¹¹</td>
<td>r, db, mc,</td>
<td>527 (256)</td>
<td>Ga: 400 mg oral od Ga: 400 mg oral od Cl: 500 mg oral bid</td>
<td>5</td>
<td>Ga: 135/151 (89.0%)</td>
<td>Ga: 85/87 (97.7%) Ga: 75/80 (93.8%) CL: 87/89 (97.8%)</td>
</tr>
<tr>
<td>DeAbate et al 1999¹²</td>
<td>r, db, mc, mn</td>
<td>211 (84)</td>
<td>Ga: 400 mg oral od Cx: 250 mg oral bid</td>
<td>7-10</td>
<td>Ga: 76/85 (89.4%) 95% CI (0.7, 22.0)</td>
<td>Ga: 37/41 (90.2%) Cx: 33/43 (76.7%)</td>
</tr>
<tr>
<td>Shah et al 1999¹³</td>
<td>r, db, dd, mc</td>
<td>832 (348)</td>
<td>L: 250 mg oral od L: 500 mg oral od Cx: 250 mg oral bid</td>
<td>7-10</td>
<td>L: 121/156 (77.6%) Cx: 108/137 (78.8%) 95% CI (-3.3, 22.5)</td>
<td>L: 88/127 (69.3%) 95% CI (-4.0, 30.0) Cx: 68/114 (59.6%)</td>
</tr>
<tr>
<td>DeAbate et al 1997¹⁴</td>
<td>r, db</td>
<td>124 (124)</td>
<td>L: 250 mg oral od L: 500 mg oral od</td>
<td>7</td>
<td>L: 26/41 (63.4%)</td>
<td>L: 28/41 (68.3%) Cx: 20/42 (47.6%)</td>
</tr>
</tbody>
</table>

#### Notes

- *Clinical outcome is defined as the primary clinical efficacy parameter as denoted in each study.
- *Microbiology outcome is defined as the effectiveness measured in the microbiologically valid population at the evaluation of primary clinical efficacy.
- *95% confidence interval for 5-day moxifloxacin therapy versus 10-day clarithromycin therapy.
- *95% confidence intervals for gatifloxacine 400 mg daily for 5 days, and gatifloxacine 400 mg daily for 7 days, respectively, vs clarithromycin 500 mg.
- *95% confidence intervals for levofloxacine 250 mg and levofloxacine 500 mg, respectively, versus cefuroxime axetil 250 mg.
- *Combined clinical and microbiological evaluation 1 week after end of therapy.
main pathogens above, plus *Staphylococcus aureus* and atypicals, ie, *Mycoplasma pneumoniae, Chlamydia pneumoniae*, and *Legionella pneumophila*.

Traditionally, ampicillin, tetracycline-doxycycline, broad-spectrum macrolides, second- or third-generation cephalosporin, or TMP/SMX have been antimicrobials of choice for treatment of AECB and CAP. Increasing resistance to these agents has raised concerns about their continued effectiveness, however, particularly to other classes of antibiotics.

Recent data have confirmed the rise in bacterial resistance among isolates of *S pneumoniae* and other community-acquired pathogens affecting the respiratory tract. Surveillance studies in the United States,\(^5\) Canada,\(^6\) and other countries\(^3\) all report decreases in activity for penicillin, macrolides, and TMP/SMX while activity for the newer fluoroquinolones and combination beta-lactam and beta-lactamase inhibitors remained high.

The latest results of the Canadian Respiratory Organism Susceptibility Study elucidated antimicrobial resistance trends between 1997 and 2002 for 6991 unique isolates of *S pneumoniae*.\(^1\) Of the isolates tested, 20.2% were not susceptible to penicillin, and those organisms were more likely than penicillin-susceptible strains to also be resistant to other classes of antibiotics.

Over the last 3 years of the 5-year study, the proportion of penicillin-resistant *S pneumoniae* increased from 2.4% to 13.8%. Yet over the full 5-year observation period, the proportion of multi–drug-resistant *S pneumoniae* increased from 2.7% to 8.8%. Levels of macrolide resistance were approximately 10% with a notable 40% increase in resistant clinical isolates over 5 years. Apart from macrolides, the largest incidence of resistance was found for TMP/SMX at 19%. Fluoroquinolone resistance among *S pneumoniae* was low (<1.2%); the most active was *Cefuroxime axetil*, IV—intravenous, L—levofloxacin, M—moxifloxacin, mc—multicentre, mn—multinational, ol—open label, r—randomized.

\(^*\)Clinical outcome is defined as the primary clinical efficacy parameter as denoted in each study.

\(^1\)Microbiology outcome is defined as the effectiveness measured in the microbiologically valid population at the evaluation of primary clinical efficacy.

\(^2\)Combined comparator (CC) group efficacy; patients treated with amoxicillin (41/244), clarithromycin (60/244), and amoxicillin and clarithromycin (143/244).
were not susceptible to macrolides, a 21.9% increase over values reported in 2000. Resistance to respiratory fluoroquinolones, telithromycin, and ceftriaxone was rare.

Resource use and patients’ quality of life
A cost-effectiveness analysis has been reported for an empiric CAP trial in Europe in which moxifloxacin was compared with intravenous amoxicillin and oral clavulanate administered 3 times daily together with clarithromycin twice daily. Moxifloxacin therapy resulted in a 5.3% higher clinical cure rate 5 to 7 days after cessation of therapy (95% CI 1.2-11.8), more rapid return to an afebrile state (P = .008) and a reduction in length of hospital stay by 0.81 days (95% CI -0.01-1.63). Primarily driven by the shorter hospital stay, total treatment cost savings per patient were $441 (Germany), $632 (France), $466 (Spain), and $576 (UK). The probability that moxifloxacin therapy reduces costs ranged from 87% (UK) to 97% (Germany).

A recent US study evaluated the effect of implementing in a rural hospital guidelines from the Infectious Diseases Society of America on community-acquired pneumonia. The percentage of patients receiving appropriate antibiotic therapy increased from 67% to 87%, and significantly more antibiotic orders met CAP guideline criteria within 2 hours of patient hospital admission. The mean length of hospital stay decreased by 1 day, and the average charge per patient decreased by $829 (US) in the postintervention group. Comparison of antibiotic distribution before and after intervention revealed use of beta-lactam and beta-lactamase inhibitors remained constant (6.9% to 7.0%); cephalosporin use decreased slightly (37.7% to 32.4%); treatment with clindamycin decreased (6.6% to 4.6%); and macrolide use was more markedly reduced (18.6% to 11.6%) while fluoroquinolone therapy increased from 30.2% to 44.4% (P = .0003). Thus, adherence to guidelines improved antibiotic prescribing habits and patient outcomes.

In a multicentre CAP trial, sequential levofloxacin therapy was compared with usual practice. Effectiveness was measured by a standard health-related quality-of-life protocol, and resource use was measured by the number of bed days per patient managed. The principal outcome was that, despite more severe disease among levofloxacin-treated patients, they required 1.7 fewer days of intravenous therapy (4.6 versus 7.3; P = .01). Other outcomes, while favouring fluoroquinolone therapy, were not statistically significant.

Economic assessment of the levofloxacin intervention trial calculated costs to government, health care system, and society. There were fewer hospital admissions among fluoroquinolone-treated patients than among those receiving conventional therapy both overall (46.5% versus 62.2%) and among low-risk patients (33.2% versus 46.8%; P < .001). Hospitals employing fluoroquinolone therapy had fewer bed days per patient and used fewer inpatient medical resources. Cost savings due to fluoroquinolone therapy from all perspectives ranged from $457 (US) to $994 (US) per patient.

Similar trends among fluoroquinolone-treated AECB patients have also been reported from the Gemifloxacin Long-term Outcomes in Bronchitis Exacerbations study. Relative to clarithromycin there were fewer hospitalizations related to respiratory tract infections, shorter lengths of stay, and larger mean per-patient cost savings for the fluoroquinolone treatment arm. Patients receiving fluoroquinolone therapy reported better quality-of-life scores and fewer consequences of AECB affecting work performance or their ability to carry out their usual activities.

Discussion
The most recent management guidelines for AECB and CAP advocate the use of newer quinolone agents as targeted and effective antimicrobial therapy in defined subsets of both AECB and CAP patients. This position is supported by clinical trial data including clinical and bacteriological outcome measures, pharmacokinetic and pharmacodynamic parameters, and safety profile.

Respiratory fluoroquinolones are highly active against the agents responsible for both AECB and CAP. Multinational consensus groups recommend either of these drugs as a first choice for empiric use among patients at risk of treatment failure or of hospitalization. Targeted use of respiratory fluoroquinolones has been shown to reduce morbidity and mortality and shorten or prevent hospitalizations and thereby reduce attendant health care costs. Faster symptom resolution, better clinical outcomes, and less patient morbidity have been observed among patients treated with beta-lactam or macrolide antibiotics, which are potent agents against both susceptible and resistant pathogens.

The safety of fluoroquinolones compares favourably with that of other antimicrobial classes. Commonly reported adverse events are for the most part mild and reversible and affect the central nervous system, gastrointestinal tract, and skin. A recent additional class effect involves QTc prolongation in predisposed patients, similar to that observed with macrolides.

Recent Canadian data from large, multicentre surveillance initiatives have been used to monitor resistance trends among clinical isolates of S pneumoniae. Rates of antimicrobial resistance among clinical pneumococcal isolates continued to grow relative to previous benchmarks; penicillin- and macrolide-resistant S pneumoniae was the principal cause of the observed increase. In contrast, the rate of resistance in Canada to respiratory fluoroquinolones appeared stable at <1% over the
latest 3-year observational period, which is consistent with rates of resistance reported from US, European, and global surveillance initiatives.

Fluoroquinolone resistance among pneumococci is primarily caused by mutations in the quinolone resistance-determining regions of \textit{parC} and \textit{gyrA} genes that encode subunits of type II topoisomerases.\textsuperscript{42, 43} Isolates that are ciprofloxacin-resistant but susceptible to levofloxacin, gatifloxacin, and moxifloxacin usually have only a first-step \textit{parC} mutation.\textsuperscript{44-46} Most levofloxacin-resistant pneumococci have mutations in both \textit{parC} and \textit{gyrA} and are not susceptible to gatifloxacin and moxifloxacin.\textsuperscript{44-46}

Mutations in \textit{parC} are much more common than those in \textit{gyrA}, most likely resulting from broad use of ciprofloxacin and levofloxacin, for which \textit{parC} is the principal bacterial target. Gatifloxacin and moxifloxacin preferentially target \textit{gyrA}, in which mutations are known to arise at a lower rate than in \textit{parC}.\textsuperscript{47}

The population of isolates with first-step mutations in \textit{parC} is important because they are more likely than pneumococci without \textit{parC} mutations to develop resistance to most quinolone agents during therapy by acquisition of a second-step \textit{gyrA} mutation.\textsuperscript{48} Therefore, despite reported low levels of in vitro pneumococcal resistance, the prevalence of clinical strains of \textit{S. pneumoniae} harbouring \textit{parC} mutations is increasing. Prudent use of fluoroquinolones that preferentially target \textit{gyrA} would alleviate bacterial selection pressure and prolong the clinical utility of this antimicrobial class.

**Conclusion**

Respiratory fluoroquinolones demonstrate excellent in vitro activity against a variety of pathogens infecting the respiratory tract. Current data support the use of these agents in treatment of lower respiratory tract infections, specifically AECB and CAP. Several well-controlled clinical trials have demonstrated the higher clinical efficacy and superior bacteriological eradication rates of respiratory fluoroquinolones compared with macrolides and beta-lactams. A growing body of evidence supports respiratory fluoroquinolones as first-choice agents for the treatment of high-risk AECB or CAP patients. Judicious and targeted use of respiratory fluoroquinolones in the at-risk patient populations specified in current AECB and CAP treatment guidelines should contribute to improved clinical outcomes and broader health care savings.

**Competing Interests**

None declared

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**References**


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