Fluoroquinolones compared with β-lactam antibiotics for the treatment of acute bacterial sinusitis: a meta-analysis of randomized controlled trials

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ABSTRACT

Background: The presumed superiority of newer fluoroquinolones for the treatment of acute bacterial sinusitis is based on laboratory data but has not yet been established on clinical grounds.

Methods: We performed a meta-analysis of randomized controlled trials comparing the effectiveness and safety of fluoroquinolones and β-lactams in acute bacterial sinusitis.

Results: We identified 8 randomized controlled trials investigating the newer “respiratory” fluoroquinolones moxifloxacin, levofloxacin and gatifloxacin. In the primary effectiveness analysis involving 2133 intention-to-treat patients from 5 randomized controlled trials, the extent of clinical cure and improvement did not differ between fluoroquinolones and β-lactams (odds ratio [OR] 1.09, 95% confidence interval [CI] 0.85–1.39) at the test-of-cure assessment, which varied from 10 to 31 days after the start of treatment. Fluoroquinolones were associated with an increased chance of clinical success among the clinically evaluable patients in all of the randomized controlled trials (OR 1.29, 95% CI 1.03–1.63) and in 4 blinded randomized controlled trials (OR 1.45, 95% CI 1.05–2.00). There was no statistically significant difference between fluoroquinolones and amoxicillin–clavulanate (OR 0.99–1.65). Eradication or presumed eradication of the pathogens isolated before treatment was more likely (OR 1.24, 95% CI 0.93–1.65) and in 4 blinded randomized controlled trials (OR 2.11, 95% CI 1.09–4.08). In the primary safety analysis, adverse events did not differ between treatments (OR 1.17, 95% CI 0.86–1.59). However, newer, third- and fourth-generation fluoroquinolones possess excellent in vitro activity against the most common respiratory pathogens, and for this reason these drugs are often designated as “respiratory.” Based on analysis of the available laboratory data, current guidelines give the newer fluoroquinolones the highest ranking, in terms of expected clinical effectiveness, among the antimicrobials used to treat acute bacterial sinusitis (although admittedly the difference is marginal).

Interpretation: In the treatment of acute bacterial sinusitis, newer fluoroquinolones conferred no benefit over β-lactam antibiotics. The use of fluoroquinolones as first-line therapy cannot be endorsed.

Acute bacterial sinusitis (more accurately known as rhinosinusitis, given that the nasal mucosa is commonly involved) is one of the most frequent health disorders; it has an adverse impact on patients’ quality of life and accounts for nearly 3 million ambulatory care visits in the United States annually and substantial health care costs.

The presumed clinical advantage of the respiratory fluoroquinolones over other classes of antimicrobials has not been clearly demonstrated in comparative clinical trials or meta-analyses. We aimed to comprehensively reassess the role of fluoroquinolones in the treatment of acute bacterial sinusitis, in terms of effectiveness and safety, by performing a meta-analysis of relevant randomized controlled trials.
Methods

Data sources
We searched MEDLINE (from July 1965 to March 2007) for potentially relevant randomized controlled trials comparing fluoroquinolone antibiotics and β-lactams in the treatment of acute bacterial sinusitis. We chose β-lactam antibiotics as the comparator treatment because they constitute a well-established treatment option for acute bacterial sinusitis, they are frequently used in clinical practice, and they retain sufficient in vitro activity against common respiratory pathogens, and they are among the agents with the highest expected clinical effectiveness, as recommended in current treatment guidelines. The following search strategy was used: “quinolones AND (sinusitis OR rhinosinusitis OR sinus infection).” We subsequently performed searches in the Scopus database and in the Cochrane Central Register of Controlled Trials to retrieve additional articles that might qualify for inclusion in our meta-analysis. Finally, the bibliographies of retrieved articles were hand-searched for references relevant to the subject of our meta-analysis.

Study selection criteria
Studies eligible for inclusion were randomized controlled trials comparing fluoroquinolone antibiotics with β-lactam antibiotics, in terms of effectiveness or safety, for the treatment of acute bacterial sinusitis. Trials involving patient populations with different clinical conditions were included only if they reported separately the data for patients with acute bacterial sinusitis or if the percentage of patients with acute bacterial sinusitis was greater than 70%. Trials in languages other than English, French, German, Italian or Greek were not included in this meta-analysis.

For trials to be considered for inclusion in the meta-analysis, the diagnosis of acute bacterial sinusitis for patient enrollment had to have been based primarily on clinical criteria, whether or not further supported by radiologic or microbiologic criteria. The clinical diagnostic criteria used in each trial had to be in accord with the following definition of acute bacterial sinusitis: a disorder lasting no more than 28 days and comprising a constellation of signs and symptoms such as nasal congestion, purulent discharge, postnasal drip, facial pain or pressure, alteration in the sense of smell, fever, headache, cough, dental pain and halitosis.

Data extraction
Two reviewers (A.P.G. and K.P.G.) independently evaluated all retrieved articles, on the basis of title and abstract, for eligibility for inclusion in the meta-analysis. The full text of potentially relevant articles was reviewed in detail.

The articles selected for inclusion were indexed and tabulated on the basis of first author, year of the study and country where the study took place. Data referring to the characteristics of each trial were extracted, including type and funding of study; definition of study population; patient inclusion and exclusion criteria; mean age and sex distribution of the study groups; numbers of patients enrolled, randomly assigned to treatment groups and evaluated; type, dosage and duration of study treatments; and use of additional medications. Also recorded were data referring to the definition of outcomes used in each study, the methods for evaluating the various outcomes and the time of the evaluation, as well as the actual measures of effectiveness and safety of the study treatments. Any differences between the 2 reviewers in terms of data extracted were resolved by discussion among all of the authors.

Outcomes of the meta-analysis
The primary comparison in this meta-analysis involved respiratory fluoroquinolones (defined as fluoroquinolones with enhanced activity against S. pneumoniae, which are recommended for the treatment of acute bacterial sinusitis) versus β-lactam antibiotics. A secondary comparison involved all fluoroquinolones versus β-lactam antibiotics.

The primary effectiveness outcome of this meta-analysis was clinical success, which combined cure (according to clinical criteria) and substantial improvement in symptoms related to acute bacterial sinusitis, in the intention-to-treat population, defined as patients who were randomly assigned to receive a study treatment. The time of determination of the primary effectiveness outcome in each trial was termed the test-of-cure time point. The primary safety outcome of this meta-analysis was defined as the total number of adverse events recorded in patients who were evaluated for this outcome in the included trials.

The secondary effectiveness outcomes of the meta-analysis were the clinical success in the clinically evaluable population assessed at the test-of-cure time point of each included trial, and within a timeframe of 21 days since the beginning of study treatments, and the bacteriologic success of the bacteriologically evaluable population, defined as eradication or presumed eradication of the pathogens isolated before treatment through direct puncture of the paranasal sinuses or endoscopic sampling methods. The clinically evaluable population consisted of patients fulfilling the criteria for clinical evaluation, and the bacteriologically evaluable population consisted of patients fulfilling the criteria for bacteriologic evaluation, according to the criteria used in each study.

The secondary safety outcomes were the number of severe adverse events, as reported by the study investigators, the number of withdrawals from studies because of adverse events, and the number of relapses, defined by the reappearance of symptoms related to acute bacterial sinusitis after initial resolution. In addition, the specific types of adverse events for each treatment group that were most commonly reported in the included trials were pooled.

Subset and sensitivity analyses
We performed a subset analysis to compare respiratory fluoroquinolones with amoxicillin–clavulanate, in terms of clinical success at the test-of-cure time point, in the clinically evaluable population. Sensitivity analyses assessed the clinical success in the clinically evaluable population at test-of-cure time point, as well as total adverse events, in studies with a double-blind or an investigator-blinded design.
Quality assessment
The randomized controlled trials included in the meta-analysis were assessed for methodologic quality by considering the following parameters: reporting of adequate randomization procedures, allocation concealment, masking of the intervention, reporting of study withdrawals, reporting of patient crossovers between treatment arms and reporting of violation of the inclusion criteria.

Data analysis and statistical methods
For all statistical analyses performed, we calculated pooled odds ratios (ORs) and 95% confidence intervals (CIs) using the Mantel–Haenszel fixed-effects model or, in the case of substantial statistical heterogeneity among the results of different studies, the DerSimonian–Laird random-effects model. We assessed statistical heterogeneity between trials using the $\chi^2$ statistic or, if no heterogeneity was detected by this method, the I$^2$ statistic. We assessed publication bias by means of the funnel plot method using Egger’s test.

Results
Selected trials
We initially screened 191 articles that were retrieved from the MEDLINE database after application of the search criteria. Of these, 9 randomized controlled trials fulfilled the criteria for inclusion in our meta-analysis. Two additional trials eligible for inclusion were detected after a secondary search on the Scopus database, but no additional trials were identified in the Cochrane Central Register of Controlled Trials. A total of 11 trials were included in the meta-analysis (Figure 1). The 2 reviewers independently reached the same conclusions regarding studies to be included.

Characteristics of the selected trials
The characteristics of the selected trials, specifically the type of trial, inclusion criteria used, definition of the study population, mean age and sex distribution of patients, numbers of patients enrolled and randomly assigned to treatment, and details of the treatments compared, are presented in Appendix 1 (available online at www.cmaj.ca/cgi/content/full/178/7/845/DC2).

Eight of the 11 trials compared respiratory fluoroquinolones (specifically moxifloxacin [4 trials], levofloxacin [3 trials] or gatifloxacin [1 trial]) with β-lactams. The remaining 3 trials investigated other fluoroquinolones (specifically ciprofloxacin [2 trials] and sparflxacin [1 trial]). The β-lactam comparators used in these trials were amoxicillin combined with clavulanic acid (5 trials), cefuroxime axetil (5 trials) and cefdinir (1 trial). All but 1 of the randomized controlled trials included in the meta-analysis had 2 treatment arms; the exception compared short-course (5-day) gatifloxacin treatment with standard-duration (10-day) gatifloxacin treatment and with amoxicillin–clavulanate treatment. We used the data for the standard-duration gatifloxacin treatment arm in this meta-analysis. In addition to the treatments being compared in these studies, adjunctive medications for symptomatic relief, mostly decongestants, antihistamines and analgesics, were permitted in 8 of the trials. Two of these trials reported the percentage of patients using such medications: 76% in one study and 83.5% in the other.

Of the 11 randomized controlled trials included in this meta-analysis, 5 were open-label trials, 5 had a double-blind design, and 1 had an investigator-blinded design (see Appendix 1, available at www.cmaj.ca/cgi/content/full/178/7/845/DC2).

Adequate randomization procedures were reported in 6 of the 11 trials, allocation concealment was reported in 5 trials, and masking of the intervention was reported in 5 trials. Information on patient withdrawals from the trials was reported in 7 trials. Crossovers of patients between treatment arms were reported in 1 trial, and violation of the inclusion criteria was reported in 4 trials.

In 10 of the 11 trials, the fluoroquinolone was the experimental treatment and the β-lactam antibiotic the comparator; in the other trial, the fluoroquinolone (levofloxacin) served as the comparator; and, in this trial, the fluoroquinolone (gatifloxacin) served as the comparator.
the control treatment for an evaluation of the cephalosporin cefdinir. All but one of the included trials were designed to show statistical equivalence or noninferiority between the compared treatments; the exception was by far the smallest trial (in terms of number of patients enrolled) and therefore could not have been adequately powered to show superiority. Finally, for all of the trials except one, for which relevant data were not reported, either financial support was received from associated pharmaceutical companies or some of the authors were affiliated with the companies.

Among the patients included in the trials, the mean age was 41.1 years, and 62.6% of the patients were women. All of the trials involved outpatients with presumed acute bacterial sinusitis; 2 of the trials also enrolled patients with acute exacerbation of chronic sinusitis, but these patients represented less than 30% of the whole patient group. In addition, 3 of

| Clinical success | OR (95% CI) |
|------------------|-------------|
| **Intention-to-treat population** | |
| Respiratory fluoroquinolones | 1.09 (0.85–1.39) |
| **Clinically evaluable population** | |
| Respiratory fluoroquinolones* | 1.29 (1.03–1.63) |
| All fluoroquinolones* | 1.24 (1.03–1.49) |
| Respiratory fluoroquinolones v. amoxicillin-clavulanate | 1.24 (0.93–1.65) |
| **Blinded randomized controlled trials** | |
| Respiratory fluoroquinolones* | 1.45 (1.05–2.00) |
| All fluoroquinolones* | 1.36 (1.04–1.77) |
| **Clinical success within 10–21 d** | |
| Respiratory fluoroquinolones* | 1.39 (1.02–1.88) |
| All fluoroquinolones* | 1.32 (1.03–1.71) |
| **Bacteriologic success** | |
| Respiratory fluoroquinolones* | 2.11 (1.09–4.08) |
| All fluoroquinolones* | 1.99 (1.24–3.19) |

| Relapse | OR (95% CI) |
|---------|-------------|
| Respiratory fluoroquinolones | 0.79 (0.47–1.33) |

| Adverse events | |
|----------------|-------------|
| Respiratory fluoroquinolones | 1.17 (0.86–1.59) |
| All fluoroquinolones | 1.16 (0.95–1.40) |
| **Blinded randomized controlled trials** | |
| Respiratory fluoroquinolones* | 1.54 (1.19–2.00) |
| All fluoroquinolones* | 1.33 (1.09–1.63) |
| **Severe adverse events** | |
| Respiratory fluoroquinolones* | 0.53 (0.30–0.95) |
| All fluoroquinolones* | 0.53 (0.30–0.93) |
| **Withdrawals** | |
| Respiratory fluoroquinolones | 1.35 (0.94–1.95) |
| All fluoroquinolones | 1.17 (0.88–1.56) |

Figure 2: Pooled odds ratios (ORs) and 95% confidence intervals (CIs) of comparisons of effectiveness and safety between fluoroquinolones and β-lactam antibiotics. In both forest plots, an OR greater than 1 indicates an increased likelihood of the outcome with fluoroquinolone therapy. In the upper forest plot, an OR greater than 1 favours fluoroquinolone therapy; in the lower forest plot, an OR greater than 1 favours β-lactam therapy. An asterisk indicates a statistically significant difference. The vertical line represents no difference between compared treatments. See Methods for descriptions of each comparison.
the included studies reported that a large number of the patients had a history of allergic rhinitis.

The diagnosis of acute bacterial sinusitis was based on various clinical criteria; radiologic criteria were also used in 8 of the trials (see Appendix 1, available at www.cmaj.ca/cgi/content/full/178/7/845/DC2).

**Time of determination of primary effectiveness outcome**

The time of determination of the primary effectiveness outcome (i.e., the time of the test-of-cure visit for the assessment of clinical success in each trial) varied from 10 to 31 days after the beginning of study treatment (see Appendix 2, available at www.cmaj.ca/cgi/content/full/178/7/845/DC2).

**Evaluation of outcomes**

Five of the studies, all involving respiratory fluoroquinolones, reported data on the clinical effectiveness of treatments in the intention-to-treat population, and all 11 studies reported relevant data regarding the clinically evaluable population. The criteria defining the clinically evaluable population consisted mainly of the requirement for adequate compliance with the assigned antimicrobial treatment, lack of use of additional antibiotics unless a clinical failure was noted and availability of the patient for the test-of-cure evaluation. By these criteria, 85.9% of the intention-to-treat population in the fluoroquinolone groups and 86.6% of the intention-to-treat population in the β-lactam groups were clinically evaluable.

The criteria used to define clinical cure or improvement, the primary outcome of this meta-analysis, differed among the studies (see Appendix 2, available at www.cmaj.ca/cgi/content/full/178/7/845/DC2). For example, in 6 of the 11 trials, the resolution of signs and symptoms of acute sinusitis had to be accompanied by resolution of the radiographic findings. Two of the studies provided no data on the combined outcome of cure or improvement but did report data on the complete resolution of signs and symptoms. Despite these differences, we entered all available relevant data in the analysis of the primary outcome.

**Comparisons of effectiveness**

Appendix 2 (available at www.cmaj.ca/cgi/content/full/178/7/845/DC2) presents the detailed data that we considered for the analyses of effectiveness and safety of the compared treatments. Figure 2 presents the pooled ORs and 95% CIs for all of the analyses performed. Detailed results for each of the analyses are presented in the following text.

**Clinical success**

All of the 5 studies that provided specific relevant data for the analysis of clinical success in the intention-to-treat population compared respiratory fluoroquinolones with β-lactam antibiotics. No statistically significant difference was observed between treatment groups at the test-of-cure time point (fixed-effects model for data from 5 randomized controlled trials with a total of 2133 patients, OR 1.09, 95% CI 0.85–1.39) (Figure 3).

Among the clinically evaluable patients, those who received respiratory fluoroquinolones (moxifloxacin, levofloxacin or gatifloxacin) had a greater chance of clinical success than those given β-lactams, as assessed at the test-of-cure time.
point (fixed-effects model for 8 trials with a total of 2797 patients, OR 1.29, 95% CI 1.03–1.63) (Figure 4). The same was true for patients who received any fluoroquinolone (including ciprofloxacin and sparflaxin) relative to those given β-lactams (fixed-effects model for 11 trials with a total of 4640 patients, OR 1.24, 95% CI 1.03–1.49) (Figure 4).

Clinically evaluable patients had a greater chance of clinical cure or improvement within 21 days after the start of study treatments if they received a respiratory fluoroquinolone rather than β-lactam treatment (fixed-effects model for 5 trials with a total of 1758 patients, OR 1.39, 95% CI 1.02–1.88). The same was true for patients who received any fluoroquinolone rather than β-lactam treatment (fixed-effects model for 7 trials with a total of 2382 patients, OR 1.32, 95% CI 1.03–1.71).

In the sensitivity analysis, limited to the double-blinded or investigator-blinded randomized controlled trials, clinically evaluable patients had a greater chance of clinical success if they were given a fluoroquinolone rather than a β-lactam, both in the comparison of respiratory fluoroquinolones with β-lactams (fixed-effects model for 4 trials with a total of 1402 patients, OR 1.45, 95% CI 1.05–2.00) and in the comparison of all fluoroquinolones with β-lactams (fixed-effects model for 6 trials with a total of 2026 patients, OR 1.36, 95% CI 1.04–1.77).

We found no statistically significant difference in clinical success between clinically evaluable patients given a respiratory fluoroquinolone and those given amoxicillin–clavulanate (fixed-effects model for 5 trials with a total of 1663 patients, OR 1.24, 95% CI 0.93–1.65).

Bacteriologic success
Eradication or presumed eradication of pathogens that were isolated before treatment was more likely if patients received a respiratory fluoroquinolone rather than a β-lactam (fixed-effects model for 3 trials with a total of 506 patients, OR 2.11, 95% CI 1.09–4.08) or if they received any fluoroquinolone rather than a β-lactam (fixed-effects model for 5 trials with a total of 868 patients, OR 1.99, 95% CI 1.24–3.19).

Relapse
Data for relapse of signs and symptoms of sinusitis were available only from trials that compared respiratory fluoroquinolones and β-lactams. We found no statistically significant difference in terms of relapse, as recorded by patients’ follow-up visits (fixed-effects model for 4 trials with a total of 1599 patients, OR 0.79, 95% CI 0.47–1.33).

Comparisons of safety
Adverse events
The rate of adverse events did not differ significantly between patients given a respiratory fluoroquinolone and those who received a β-lactam (random-effects model for 6 trials with a total of 2732 patients, OR 1.17, 95% CI 0.86–1.59) (Figure 5). The same was true for patients given any fluoroquinolone relative to those given a β-lactam (random-effects model for 9 trials with a total of 5018 patients, OR 1.16, 95% CI 0.95–1.40) (Figure 5). The specific types of adverse events reported for

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**Study** | Fluoroquinolones (n/N) | β-lactams (n/N) | OR (95% CI) |
---|---|---|---|
**Respiratory** fluoroquinolones v. β-lactams | | | |
Adelglass et al27 | 236/267 | 234/268 | 1.11 (0.66–1.86) |
Burke et al28 | 200/223 | 209/234 | 1.04 (0.57–1.89) |
Siegert et al26 | 204/211 | 204/225 | 3.00 (1.25–7.21) |
Rakkar et al25 | 146/170 | 144/171 | 1.14 (0.63–2.07) |
Sher et al24 | 101/127 | 101/141 | 1.54 (0.87–2.71) |
Henry et al22 | 101/118 | 102/123 | 1.22 (0.61–2.45) |
Jareoncharsri et al23 | 31/34 | 22/26 | 1.88 (0.38–9.25) |
Arrieta et al21 | 211/226 | 216/233 | 1.11 (0.54–2.27) |
Subtotal | 1230/1376 | 1232/1421 | 1.29 (1.03–1.63) |

**Other fluoroquinolones v. β-lactams** | | | |
Gehanno et al31 | 134/153 | 130/149 | 1.03 (0.52–2.03) |
Weis et al30 | 559/613 | 546/606 | 1.14 (0.77–1.67) |
Johnson et al29 | 144/164 | 133/158 | 1.35 (0.72–2.55) |
Subtotal | 837/930 | 809/913 | 1.16 (0.86–1.56) |
Overall | 2067/2306 | 2041/2334 | 1.24 (1.03–1.49) |

**Figure 4:** Meta-analysis of clinical success at the test-of-cure assessment of patients fulfilling the criteria for clinical evaluation (clinically evaluable population) given either “respiratory” or other fluoroquinolones or given β-lactam antibiotics. The vertical line represents no difference between compared treatments.
patients treated with any fluoroquinolone and with β-lactams were total gastrointestinal adverse events (4 trials, 2828 patients, incremental rate 10.2% v. 9.8%), diarrhea (8 trials, 4650 patients, 3.8% v. 7.2%), nausea (7 trials, 4379 patients, 5.9% v. 3.1%), adverse events affecting the body as a whole (4 trials, 3053 patients, 5.9% v. 5.5%), abdominal pain (5 trials, 2672 patients, 2.7% v. 2.4%), vaginitis (5 trials, 1990 female patients, 1.7% v. 4.6%) and adverse events affecting the nervous system (3 trials, 2454 patients, 2.7% v. 0.9%).

In blinded randomized controlled trials, significantly more adverse events were associated with the use of respiratory fluoroquinolones than with β-lactam antibiotics (fixed-effects model for 2 trials with a total of 1030 patients, OR 1.54, 95% CI 1.19–2.00). The same was true for patients given any fluoroquinolone rather than a β-lactam antibiotic (fixed-effects model for 4 trials with a total of 1905 patients, OR 1.33, 95% CI 1.09–1.63).

Severe adverse events
Significantly fewer adverse events were assessed as severe among patients who received respiratory fluoroquinolones than among those who received β-lactams (fixed-effects model for 6 trials with a total of 2503 patients, OR 0.53, 95% CI 0.30–0.95). The same was true for patients given any fluoroquinolone rather than a β-lactam antibiotic (fixed-effects model for 7 trials with a total of 3004 patients, OR 0.53, 95% CI 0.30–0.93).

Withdrawals due to adverse events
The chances of withdrawal from the trials because of adverse events were not statistically significantly different between patients given a respiratory fluoroquinolone and those given a β-lactam antibiotic (fixed-effects model for 8 trials with a total of 3298 patients, OR 1.35, 95% CI 0.94–1.95). The same was true for patients given any fluoroquinolone rather than a β-lactam (fixed-effects model for 11 trials with a total of 5584 patients, OR 1.17, 95% CI 0.88–1.56).

Interpretation
The main finding of our meta-analysis is that the so-called respiratory fluoroquinolones did not prove superior to β-lactams for the treatment of acute bacterial sinusitis in terms of the primary effectiveness outcome (clinical success [clinical cure or improvement]) or the primary safety outcome (total adverse events). However, in some of the secondary analyses, treatment outcomes were better among patients who received a respiratory fluoroquinolone than among those given a β-lactam antibiotic, specifically in the comparison of clinically evaluable populations (patients fulfilling the criteria for clinical evaluation), in the sensitivity analysis limited to blinded randomized controlled trials, and in terms of bacteriologic success (eradication or presumed eradication of the pathogens isolated before treatment). Yet patients who received a respiratory fluoroquinolone did not have greater clinical success than those given amoxicillin–clavulanate, nor did they have fewer relapses than patients given a β-lactam antibiotic. Furthermore, in the sensitivity analysis limited to blinded randomized controlled trials, the fluoroquinolone group had more total adverse events than the β-lactam group. Still, among all the relevant studies included in our meta-analysis, treatment with fluoroquinolones resulted in fewer severe adverse events.

The aforementioned associations did not change substantially when we included randomized controlled trials compar-

| Study                  | Fluoroquinolones (n/N) | β-Lactams (n/N) | OR (95% CI) |
|------------------------|------------------------|----------------|-------------|
| **“Respiratory” fluoroquinolones** |                        |                |             |
| Adelglass et al27      | 114/297                | 146/302        | 0.67 (0.48–0.92) |
| Burke et al28          | 96/263                 | 70/274         | 1.68 (1.16–2.42) |
| Siegert et al26        | 105/242                | 88/251         | 1.42 (0.99–2.04) |
| Rakkar et al25         | 136/234                | 124/237        | 1.26 (0.88–1.82) |
| Jareoncharsri et al21  | 3/34                   | 2/26           | 1.16 (0.18–7.51) |
| Arrieta et al21        | 93/289                 | 84/283         | 1.12 (0.79–1.60) |
| Subtotal               | 547/1359               | 514/1373       | 1.17 (0.86–1.59) |
| **Other fluoroquinolones** |                        |                |             |
| Gehanno et al31        | 19/190                 | 15/184         | 1.25 (0.62–2.55) |
| Weis et al30           | 136/711                | 115/700        | 1.20 (0.92–1.58) |
| Johnson et al29        | 115/250                | 113/251        | 1.04 (0.73–1.48) |
| Subtotal               | 270/1151               | 243/1135       | 1.15 (0.93–1.41) |
| **Overall**            | 817/2510               | 757/2508       | 1.16 (0.95–1.40) |

Figure 5: Meta-analysis of adverse events reported among patients given “respiratory” or other fluoroquinolones or given β-lactam antibiotics. The vertical line represents no difference between compared treatments.
ing any fluoroquinolone with a β-lactam antibiotic in the analysis. However, ciprofloxacin and sparfloxacin, the fluoroquinolones used in these additional studies, are not regarded as being as potent against S. pneumoniae, in microbiologic terms, as the newer fluoroquinolones, and they are not currently recommended for the treatment of acute bacterial sinusitis. Nonetheless, both were approved by the US Food and Drug Administration for this indication, although sparfloxacin was withdrawn from the US market in 2001. Despite their inferior bacteriologic activity, our inclusion of ciprofloxacin and sparfloxacin in this meta-analysis may be meaningful, given that these 2 agents share certain pharmacokinetic properties with the newer respiratory fluoroquinolones, specifically with regard to drug penetration into the sinus mucosa. In addition, from a safety standpoint, most of the adverse events observed with fluoroquinolones are thought to be related to a class effect rather than an agent-specific effect.

In the remainder of this discussion, we focus on the respiratory fluoroquinolones, although many of the issues addressed may also be relevant to the comparison of all fluoroquinolones with β-lactam antibiotics.

Although fluoroquinolones were comparable to β-lactam antibiotics in terms of the effectiveness outcomes of this meta-analysis when the intention-to-treat population was examined, analysis of the clinically evaluable population showed a marginal advantage in favour of fluoroquinolone treatment. This apparent disparity can be explained by the fact that the intention-to-treat analysis generally provides a more conservative estimate of treatment effect. Moreover, data for the outcome of clinical success in the intention-to-treat population were available for only 5 of the 11 included randomized controlled trials. However, the value of the intention-to-treat analysis is that it respects the random assignment of patients to study treatments and precludes bias in the selection of patients for evaluation, which is particularly important in nonblinded trials. In addition, the nature of the intention-to-treat analysis relates more closely to therapeutic decision-making in clinical practice.

In addition to the overall rate of resolution of symptoms in cases of acute bacterial sinusitis, the rapidity of symptom resolution is also important, because this condition adversely affects quality of life and is associated with substantial loss of productivity and associated sick leave expenditures in the workplace. We therefore performed a subanalysis assessing clinical effectiveness within 3 weeks after the start of treatment, which showed a marginal benefit of fluoroquinolones over β-lactams.

Some factors might blunt the demonstration of true differences between treatments in trials of acute bacterial sinusitis. The most important such factor is the expected enrolment of many patients with self-limiting viral disease, despite the use of clinical or radiologic diagnostic inclusion criteria. In fact, in this meta-analysis, the pooled percentage of patients with bacteriologically documented disease in the trials in which relevant studies were performed was 54%. Additional factors that may confound the assessment of effectiveness of the studied treatments include the potential for sinusitis-like symptoms to persist despite bacteriologic cure and the likelihood of unbalanced use of symptom-relief medications among different treatment groups. In this regard, the greater bacteriologic success exhibited with respiratory fluoroquinolones relative to β-lactams may be important. Still, the analysis of clinical success may be the best indicator of routine clinical practice.

Among the 5779 patients enrolled in the trials included in this meta-analysis, no serious complications of sinusitis, such as orbital or intracranial spread, were reported. Although serious complications of sinusitis are rare among patients who receive appropriate treatment, the lack of such complications in the populations evaluated in this meta-analysis could be attributed to the fact that patients with a greater likelihood of a complicated course of disease (e.g., those with a history of chronic sinusitis or recurrent acute sinusitis) were excluded from a considerable number of the trials, even though they are frequently encountered in routine clinical practice. In addition, in all but one of the included studies, the duration of follow-up was limited to no more than 1 month after the end of therapy, which may have been inadequate for accurate estimation of the rates of recurrence and progression to chronic sinusitis.

From a safety standpoint, the primary analysis, which included all 11 studies, showed that the treatments were comparable in terms of total adverse events recorded. Most of the reported adverse events involved the gastrointestinal tract, with diarrhea being more frequent in the β-lactam group and nausea more frequent in the fluoroquinolones group. In the analysis of adverse events, significant statistical heterogeneity between trials was observed. This can be attributed to the findings of one trial, which had a lower rate of adverse events in the fluoroquinolone group, whereas the other trials had an opposing trend. When we omitted the one trial in a post hoc exploratory analysis, we found that adverse events were significantly more common among patients given a respiratory fluoroquinolone (fixed-effects model for 5 trials with a total of 2133 patients, OR 1.35, 95% CI 1.13–1.62) or any fluoroquinolone (fixed-effects model for 8 trials with a total of 4419 patients, OR 1.26, 95% CI 1.10–1.44) rather than a β-lactam antibiotic. In addition, in the sensitivity analysis limited to blinded randomized controlled trials, a higher rate of adverse events was associated with fluoroquinolone use than with β-lactam use. Notably, in a prior meta-analysis concerning treatment of skin and soft-tissue infections in 4352 patients, the use of fluoroquinolones was associated with significantly more adverse events than β-lactam use was.

Nevertheless, adverse events characterized as severe were significantly less frequent among patients given a fluoroquinolone than among those given a β-lactam antibiotic. No cases of major arrhythmia, hepatitis, seizure or severe phototoxicity reaction, all of which are potentially serious adverse events associated with the use of some fluoroquinolones, were recorded among patients included in this meta-analysis. However, the absence of these adverse events could be partly attributed to the exclusion from clinical trials of patients who are prone to experience a serious adverse event associated with the study drugs. In fact, in 4 of the 11 trials included in

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this meta-analysis, patients were excluded if they had a history of seizure disorder, fluoroquinolone-related tendinopathy or a prolonged QRS interval. Moreover, some severe adverse events may be so rare that they will be identified only in large-scale postmarketing surveillance programs. This was the case for gatifloxacin, which has been withdrawn from the market because of its association with disturbances in glucose control. This drug was studied in only one of the trials included in our meta-analysis, and no adverse event of this type was reported among the 290 patients in the gatifloxacin group in that trial.

Issues relating to bacterial drug resistance are also important in the choice of antimicrobial therapy. In fact, the major “respiratory” pathogens (S. pneumoniae, H. influenzae and M. catarrhalis) have acquired resistance to multiple antibiotics, to various degrees. Of great concern is the increased prevalence of S. pneumoniae with reduced susceptibility to penicillin and, in parallel, increased resistance to other classes of antimicrobial agents. Although pneumococcal resistance to penicillin is relative and can be overcome with high-dose amoxicillin therapy in patients with sinusitis, the respiratory fluoroquinolones constitute a valuable therapeutic option. However, indiscriminate fluoroquinolone use may promote fluoroquinolone resistance in S. pneumoniae, which is often associated with multiple-drug resistance.

Our meta-analysis had certain potential limitations. First, in most meta-analyses of this kind, there was some variability in the characteristics of the included studies, relating chiefly to inclusion and evaluation criteria and the time of determination of the outcomes. Even so, for most of the analyses, the data retrieved did not exhibit significant heterogeneity. In addition, most of the included randomized controlled trials had some methodologic shortcomings. Moreover, the majority of the included trials, including all 5 of the non-blinded studies, were supported by pharmaceutical companies associated with the fluoroquinolone agents tested, a factor that may have generated bias in the assessment of outcomes. In this regard, the findings in the analysis of the blinded randomized controlled trials should be underscored.

Despite these limitations, the value of this meta-analysis lies in its combination of data from several randomized controlled trials, based on a non-inferiority design, which resulted in demonstration of differences in some aspects of the effectiveness and safety of the treatments. Most of the differences observed were of marginal statistical significance, and a randomized controlled trial of a very large sample would be required to manifest these differences.

In conclusion, we found that respiratory fluoroquinolones were comparable to β-lactams for the treatment of acute bacterial sinusitis, in terms of the primary effectiveness outcome (clinical cure and improvement) and the primary safety outcome (total adverse events) examined. However, a propensity for more adverse events in association with fluoroquinolone use was observed in sensitivity and exploratory analyses. Thus, the use of respiratory fluoroquinolones as first-line therapy in the vast majority of patients with bacterial sinusitis, in whom the condition often has a benign clinical course, is not supported by the available evidence. The finding that presumed bacteriologic success was superior among fluoroquinolone-treated patients suggests that use of a respiratory fluoroquinolone may be considered in cases where β-lactam treatment has failed, particularly if the risk of infection with drug-resistant pathogens is a consideration.

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