Prophylaxis with Fluoroquinolones for Bacterial Infections in Neutropenic Patients: A Meta-Analysis

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We conducted a two-part meta-analysis to assess the effectiveness of fluoroquinolones for preventing bacterial infections in granulocytopenic patients who are receiving chemotherapy for malignancies. Overall, 19 randomized studies met selection criteria and were included in this meta-analysis of 2,112 patients. Thirteen studies that compared the fluoroquinolones alone with control regimens (co-trimoxazole, oral nonabsorbable antibiotics, or placebo) and six studies that compared the fluoroquinolones plus prophylaxis for bacteremia due to gram-positive bacteria with control regimens (fluoroquinolones or oral nonabsorbable antibiotics) were included in the two meta-analyses. The results of the first meta-analysis indicate that fluoroquinolones alone are effective in preventing gram-negative bacteremia (overall odds ratio [OR], 0.09; 95% confidence interval [CI], 0.05–0.16; P < .001), but not gram-positive bacteremia (OR, 1.05; 95% CI, 0.76–1.45; P = .77), fever-related morbidity (OR, 0.76; 95% CI, 0.56–1.04; P = .09), and infection-related mortality (OR, 0.79; 95% CI, 0.47–1.34; P = .40). The results of the second meta-analysis indicate that a combination of fluoroquinolones plus prophylaxis for gram-positive bacteremia (penicillin, vancomycin, or macrolides) significantly reduces the occurrence of gram-positive bacteremia (OR, 0.46; CI, 0.33–0.63; P < .001) without affecting the incidence of fever-related morbidity (OR, 0.83; 95% CI, 0.62–1.13; P = .28) and infection-related mortality (OR, 0.74; 95% CI, 0.40–1.38; P = .35).

The use of fluoroquinolones as prophylaxis for bacterial infections in neutropenic patients with cancer, which has been studied extensively, is increasing. However, the benefit of prophylaxis with these drugs is debatable [1–3]. Several studies have shown that they are efficacious in reducing the incidence of bacteremia due to gram-negative organisms, but these studies have also demonstrated selection for gram-positive organisms in recipients of the fluoroquinolones [4–31].

These observations, coupled with the well-documented emergence of staphylococcal and streptococcal infections in neutropenic patients [32, 33], prompted several investigators to evaluate the efficacy of regimens that combined quinolones with antimicrobial agents active against gram-positive cocci [34–43]. Some of these studies have shown the efficacy of combined prophylaxis in reducing the incidence of streptococcal bacteremia but have yielded controversial results with respect to other parameters of infection-related morbidity.

We conducted a two-part meta-analysis to assess the efficacy of fluoroquinolones with or without prophylaxis for gram-positive bacteremia in neutropenic patients with cancer; infection-related morbidity and mortality were used as outcomes.

Materials and Methods

Literature search. The literature for the period January 1984 through October 1994 was searched with use of MEDLINE for articles and reviews pertaining to antibacterial prophylaxis in neutropenic patients. The key words used for this purpose were neutropenia/agranulocytosis and bacterial infections. The computer search was supplemented by consulting Current Contents and the bibliographies from the articles retrieved through MEDLINE.

Protocol of the analysis. Trials were included in our analysis if they involved granulocytopenic patients receiving chemotherapy for cancer; they were randomized and compared a control regimen with fluoroquinolones alone or in combination with gram-positive prophylaxis for prevention of bacterial infections; and they assessed efficacy in terms of infection-related morbidity and mortality.

Outcomes of the analysis were bacteremia, fever, and infection-related mortality. The statistical technique we used to analyze the data required knowledge of the numbers of patients with fever and bacteremia as well as the number of patients who died of their infections. These data were available only from studies published as full-length papers, not from abstracts. We could not analyze other measures of infection-related morbidity such as the time of the first febrile episode after the onset of neutropenia and the percentage of time during which...
systemic antibiotics were given in combination with prophylaxis because these data were not reported uniformly.

Quality review. Four investigators, blinded to study titles, journals, and authors and institutions independently evaluated the quality of each article according to a modification of previously developed quality assessment instruments for use in randomized controlled trials [44, 45]. This 15-category instrument evaluates quality in study design (nine categories) and data analysis and presentation of results (six categories). The nine categories of quality assessment for study design were inclusion and exclusion criteria, number of patients excluded from the trial and the reasons for exclusion, definition of study drug and control regimens (drug, dose, timing, and duration), the extent to which patients and the study team were blinded, prognostic factors between groups, and the definition of outcome measure; the six categories for data analysis and presentation of results were documentation of dates of study, recording of patient withdrawals, display of raw data, estimation of study power for detecting true differences in treatment, recording of $P$ values and test statistics for major outcomes, and calculation of confidence intervals.

The reviewers assigned values of 0 to 1.0 for each item (0 = absent or cannot be determined, 0.5 = partial, and 1.0 = present). When there was disagreement over the quality evaluation, it was resolved by consensus. The score could range from 0 (no standard satisfied) to 15 (all standards fully satisfied).

Statistical analysis. A conventional meta-analysis was performed with use of a fixed-effect model (Mantel-Haenszel method with 95% confidence intervals for an overall odds ratio calculated according to the method of Breslow and Day) and a random-effect model (the method of Der Simonian and Laird) [46–49]. The study-specific 95% confidence intervals for the odds ratio were calculated by the method of Woolf [50]. The pooled rates for the treatment and control groups were calculated by the method of Laupacis et al. [51]. All mathematical calculations were performed by using a microcomputer program (meta.exe, version 4.38) developed by two of the authors (R. R. and A. M.).

Assessment of publication bias. The issue of publication bias [52, 53] was addressed with use of the procedure of Rosenthal [54] and Klein et al. [55], which is based on an estimation of the minimum number ($m$) of negative (or null) studies required to lead the results of the meta-analysis to a statistically nonsignificant level. The value of $m$ was calculated by the formula described by Klein et al. [55]. The $m$-negative (or null) studies are hypothetical (simulated) trials in which the treatments being compared have identical efficacy. A statistically significant meta-analysis can be reversed to insignificance only by a large value for $m$, and vice versa.

Heterogeneity assessment. The need to investigate the heterogeneity of trials subjected to a meta-analysis has recently been emphasized by Thompson [56]. We used the equations reported in the appendix of Collins et al. [57] for determining heterogeneity. While the primary meta-analytic techniques of data pooling (e.g. the fixed-effect model or the random-effect model) compare the two treatments in question, heterogeneity tests evaluate whether intertrial differences exist between patients given the same treatment. Hence, these latter tests allow a first intertrial comparison of the outcome data for all patients given the first treatment combined with a second intertrial comparison between all patients given the second treatment. When wide intertrial differences are found between the success rates within the group receiving the first treatment and/or within the group receiving the second treatment, the results of heterogeneity tests generally reach statistical significance. Significant intertrial heterogeneity may indicate that the meta-analysis was an attempt to pool a series of trials that differed too much from each other.

Results

Our literature search identified 25 randomized, controlled clinical trials dealing with fluoroquinolones as prophylaxis for bacterial infections in granulocytopenic patients. Of these trials, one study in children was excluded from the analysis [14]. Of the remaining 24 studies dealing with adults, three [11, 24, 30] were excluded because they compared fluoroquinolones, one [8] was excluded because it included a set of patients that had previously been described [7], and one [16] was excluded because the participants received other antimicrobial agents (trimethoprim-sulfamethoxazole [TMP-SMZ]) in addition to a fluoroquinolone. Tables 1 and 2 summarize the characteristics of patients in the 19 studies included in the meta-analyses.

Thirteen studies compared the fluoroquinolones alone with control regimens (TMP-SMZ, oral nonabsorbable antibiotics, or placebo), whereas six studies compared the fluoroquinolones plus prophylactic antibiotics active against gram-positive pathogens (penicillin V or penicillin G, vancomycin, or macrolides) with control regimens (fluoroquinolones alone or oral nonabsorbable antibiotics). The two groups of studies were analyzed separately.

The majority of patients had hematologic malignancies (acute leukemia, chronic myelogenous leukemia in blast crisis, or lymphoma). Six studies included patients with solid tumors. All patients had severe and prolonged neutropenia related to intensive chemotherapy (with or without autologous or allogeneic bone marrow transplantation) for malignancies. The prophylactic regimen was started when the patient became granulocytopenic or was expected to be granulocytopenic and was administered when the absolute neutrophil count fell below $796$ Cruciani et al. CID 1996;23 (October)
Table 1. Characteristics of neutropenic patients in comparative studies of fluoroquinolones as prophylaxis for bacterial infections.

<table>
<thead>
<tr>
<th>Year [reference]</th>
<th>Underlying condition(s)</th>
<th>Regimen (dosage)*</th>
<th>No. receiving fluoroquinolones/ Control regimen</th>
<th>Polyomorphonuclear neutrophil count (10⁶/mm³)</th>
<th>Duration (d) of neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986 [5]</td>
<td>AL, CML, L</td>
<td>Norfloxacin (400 mg t.i.d.) or ciprofloxacin (500 mg b.i.d.)</td>
<td>36/30</td>
<td>&lt;1,000</td>
<td>3.0</td>
</tr>
<tr>
<td>1987 [6]</td>
<td>AL</td>
<td>Ciprofloxacin (500 mg b.i.d.)</td>
<td>28/28</td>
<td>&lt;500</td>
<td>10.2</td>
</tr>
<tr>
<td>1990 [17]</td>
<td>AL</td>
<td>Ofloxacin (200 mg b.i.d.) or ciprofloxacin (500 mg b.i.d.)</td>
<td>61/27</td>
<td>&lt;500</td>
<td>13.0</td>
</tr>
<tr>
<td>1991 [25]</td>
<td>AL</td>
<td>Ofloxacin (200 mg t.i.d.)</td>
<td>70/58</td>
<td>&lt;500</td>
<td>18.9</td>
</tr>
<tr>
<td>1992 [28]</td>
<td>AL</td>
<td>Ciprofloxacin (500 mg b.i.d.)</td>
<td>117/113</td>
<td>&lt;500</td>
<td>25.6</td>
</tr>
<tr>
<td>1993 [29]</td>
<td>AL</td>
<td>Enoxacin (400 mg b.i.d.)</td>
<td>62/57</td>
<td>&lt;500</td>
<td>9.0</td>
</tr>
<tr>
<td>1994 [31]</td>
<td>AL, CML, BMT</td>
<td>Ciprofloxacin (500 mg t.i.d.)</td>
<td>63/33</td>
<td>&lt;500</td>
<td>20.6</td>
</tr>
</tbody>
</table>

NOTE. The duration of neutropenia was reported as a median value in the following studies: [5], [17], [25], and [26]; all others are mean values. AL = acute leukemia; BMT = bone marrow transplantation; CML = chronic myelogenous leukemia in blast crisis; L = lymphoma; TMP-SMZ = trimethoprim-sulfamethoxazole.

* All drugs were given orally.

gram-positive bacteremia (table 4 and figure 2). Tables 3 and 4 list the cumulative odds ratios and related 95% confidence intervals for each of the study outcomes. Figures 1 and 2 show odds ratios and 95% confidence intervals, as calculated by Woolf’s method, for individual studies.

First meta-analysis. Prophylaxis with fluoroquinolones alone was shown to significantly reduce the frequency of gram-negative bacteremia (OR, 0.09; 95% CI, 0.05–0.16; P < .001) without affecting the frequency of gram-positive bacteremia (OR, 1.05; 95% CI, 0.76–1.45; P = .7) and infection-related mortality (OR, 0.79; 95% CI, 0.47–1.34; P = .4). A trend towards reduction in the incidence of fever-related morbidity was observed for patients receiving quinolones, as compared with the control group, but this difference was not statistically significant (OR, 0.76; 95% CI, 0.56–1.04; P = .09).

Second meta-analysis. The addition of gram-positive prophylaxis to fluoroquinolone prophylaxis significantly reduced the frequency of gram-positive bacteremia (OR, 0.46; 95% CI, 0.33–0.63; P < .001) without affecting the other outcomes examined. Four of the six studies examined compared fluoroquinolones plus gram-positive prophylaxis with fluoroquinolones alone. Therefore, the majority of the patients included in this analysis (763 of 957) had the same coverage for gram-negative organisms and a similar occurrence of gram-negative bacteremia (OR, 0.80; 95% CI, 0.41–1.53; P = .5).

The inclusion of the two studies in which oral nonabsorbable antibiotics were used as the control regimens did not affect the overall result of the analysis, although in one of these studies [35], a trend favoring the quinolone group over the oral nonabsorbable group (in terms of infection-related morbidity and mortality) was observed. In terms of infection-related mortality, the pooled odds ratio and the crude and pooled rates were similar between the two treatment groups. However, in the six studies examined, gram-positive pathogens were responsible for one of 18 infection-related deaths among patients receiving combination prophylaxis and for 12 of 25 infection-related
Table 2. Characteristics of neutropenic patients in comparative studies of fluoroquinolones plus prophylaxis for gram-positive bacterial infections.

<table>
<thead>
<tr>
<th>Year [reference]</th>
<th>Underlying conditions</th>
<th>Regimen (dosage)*</th>
<th>No. receiving fluoroquinolones + gram-positive prophylaxis/no. of control regimen</th>
<th>Duration (d) of neutropenia</th>
<th>Recipients of fluoroquinolones + gram-positive prophylaxis/Recipients of control regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991 [35]</td>
<td>AL, CML, L, solid tumor, BMT</td>
<td>Pefloxacin (800 mg/d), vancomycin (800 mg/d)</td>
<td>Gentamicin (100 mg/d), tobramycin (3 million U/d), colistin (3 million U/d)</td>
<td>76/74</td>
<td>&lt;500</td>
</tr>
<tr>
<td>1991 [36]</td>
<td>AL, aplastic anemia, BMT</td>
<td>Ofloxacin (200 mg b.i.d.), amoxicillin (1 g b.i.d.)</td>
<td>Vancomycin (450 mg/d), tobramycin (450 mg/d), colistin (4.5 million U/d)</td>
<td>22/22</td>
<td>&lt;500</td>
</tr>
<tr>
<td>1993 [39]</td>
<td>AL, L, BMT</td>
<td>Ciprofloxacin (500 mg b.i.d.), amoxicillin (1 g/d)</td>
<td>Ciprofloxacin (500 mg b.i.d.)</td>
<td>27/26</td>
<td>&lt;1,000</td>
</tr>
<tr>
<td>1994 [40]</td>
<td>AL, L, solid tumor, BMT</td>
<td>Norfloxacin (400 mg t.i.d.) + iv amoxicillin G (1 million U t.i.d.) or iv vancomycin (750 mg b.i.d.)</td>
<td>Norfloxacin (400 mg t.i.d.)</td>
<td>21/22</td>
<td>&lt;500</td>
</tr>
<tr>
<td>1994 [42]</td>
<td>AL, CML, L, BMT</td>
<td>Ofloxacin (200 mg t.i.d.), roxithromycin (150 mg b.i.d.)</td>
<td>Ofloxacin (200 mg t.i.d.)</td>
<td>67/64</td>
<td>&lt;1,000</td>
</tr>
<tr>
<td>1994 [43]</td>
<td>AL, L, solid tumor, BMT</td>
<td>Pefloxacin (400 mg b.i.d.), penicillin V (500 mg b.i.d.)</td>
<td>Pefloxacin (400 mg b.i.d.), placebo (b.i.d.)</td>
<td>268/268</td>
<td>NS</td>
</tr>
</tbody>
</table>

NOTE. The duration of neutropenia was reported as a mean value in all studies except [42]. AL = acute leukemia; BMT = bone marrow transplantation; CML = chronic myelogenous leukemia in blast crisis; L = lymphoma; NS = not specified.
* All drugs were given orally unless otherwise indicated.
† Four patients with an allergy to penicillin.

Quality assessment. The average quality score was 10.1 (range, 6.0–14.0). The quality criteria most often absent were blinding of patients (14 of 19 studies), blinding of the study team (15 of 19), documentation of study dates (14 of 19), and calculation of confidence intervals (16 of 19). The four reviewers agreed on quality 93.2% of the time.

Publication bias assessment. The number of unpublished null studies that would be required to render the findings of the meta-analyses nonsignificant is 196, based on the outcome of gram-negative bacteremia in the first meta-analysis, and 28, based on the outcome of gram-positive bacteremia in the second meta-analysis.

Heterogeneity assessment. The results of heterogeneity assessment for the 13 studies with fluoroquinolones alone showed...
no intertrial heterogeneity for the outcomes of gram-negative bacteremia ($\chi^2 = 0.89; df = 12; P = .99$) and infectious mortality ($\chi^2 = 4.27; df = 12; P = .97$). On the other hand, significant intertrial heterogeneity was found for the outcomes of gram-positive bacteremia ($\chi^2 = 62.61; df = 12; P < .0001$) and fever ($\chi^2 = 43.37; df = 11; P < .0001$).

The results for the six studies with fluoroquinolones plus gram-positive prophylaxis showed no intertrial heterogeneity for the outcomes of gram-negative bacteremia ($\chi^2 = 10.31; df = 5; P = .06$), infection-related mortality ($\chi^2 = 1.86; df = 5; P = .8$), and fever ($\chi^2 = 3.02; df = 4; P = .5$). However, there was evidence of heterogeneity for the outcome of gram-positive bacteremia ($\chi^2 = 20.26; df = 5; P = .001$).

Subgroup analyses. Subgroup analyses were carried out to investigate the potential source of heterogeneity that was observed for some of the outcomes (gram-positive bacteremia and fever in the first meta-analysis, and gram-positive bacteremia in the second meta-analysis).

For the first subgroup meta-analysis, selective removal of three studies with placebo groups [7, 26, 29] had minimal influence on the results in terms of the clinical endpoints but led to a substantial reduction of heterogeneity. In this subgroup analysis, we included 10 trials in which fluoroquinolones alone were compared with TMP-SMZ or oral nonabsorbable antibiotics [5, 6, 9, 17, 21–23, 25, 28, 31]. After removal of the three studies that included placebo groups, the summary odds

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Figure 1. Cumulative odds ratios (OR) and 95% confidence intervals (CI) for clinical outcomes in 13 trials that compared fluoroquinolones alone (F) with control regimens (C) as prophylaxis for bacteremia in neutropenic patients. Trials are identified by first author and year. Favors F = reduction in incidence of bacteremia among fluoroquinolone recipients; favors C = reduction in incidence of bacteremia among recipients of control regimens. Asterisk indicates that values were not computed because frequency was zero.
Table 4. Outcomes in pooled studies that compared fluoroquinolones plus prophylaxis for gram-positive bacterial infections with control regimens in neutropenic patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Gram-negative bacteremia</th>
<th>Gram-positive bacteremia</th>
<th>Fever</th>
<th>Infection-related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluoroquinolones + GPP</td>
<td>Control regimens</td>
<td>Fluoroquinolones + GPP</td>
<td>Control regimens</td>
</tr>
<tr>
<td></td>
<td>No. of patients with</td>
<td>crude rates</td>
<td>Overall OR^{1}</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>indicated outcome/total</td>
<td>(%)</td>
<td>OR (method of Mantel-Haenszel)</td>
<td>95% CI</td>
</tr>
<tr>
<td></td>
<td>in treatment group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude rates</td>
<td>3.9 5.0</td>
<td>18.5 33.8</td>
<td>73.0 76.1</td>
<td>3.7 5.2</td>
</tr>
<tr>
<td>Overall OR^{1}</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.80 0.46</td>
<td>0.83</td>
<td>0.62 1.13</td>
<td>0.40 1.38</td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>&lt;.01</td>
<td>.2</td>
<td>.3</td>
</tr>
</tbody>
</table>

NOTE. GPP = gram-positive prophylaxis.

* Pooled rates of meta-analysis (method of Laupacis et al [51]).

^{1} Overall OR (method of Mantel-Haenszel); overall ORs and 95\% CIs (method of DerSimonian and Laird [48]), respectively, are as follows: gram-negative bacteremia, 0.62 and 0.36–1.44; gram-positive bacteremia, 0.31 and 0.14–0.66; fever, 0.83 and 0.61–1.13; and infection-related mortality, 0.88 and 0.19–1.57.

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**Figure 2.** Cumulative odds ratios (OR) and 95\% confidence intervals (CI) for clinical outcomes in six trials that compared fluoroquinolones plus gram-positive prophylaxis with control regimens (C) as prophylaxis for bacteremia in neutropenic patients. Trials are identified by first author and year. EORTC = European Organization for Research and Treatment of Cancer; favors F = reduction in incidence of bacteremia among fluoroquinolone recipients; favors C = reduction in incidence of bacteremia among recipients of control regimens.
rations for the outcomes were as follows: gram-negative bacteremia, 0.08 (95% CI, 0.04–0.17; \( P < .001 \)); gram-positive bacteremia, 1.13 (95% CI, 0.78–1.64; \( P = .3 \)); fever, 0.72 (95% CI, 0.52–1.02; \( P = .06 \)); infection-related mortality, 0.72 (95% CI, 0.4–1.2; \( P = .2 \)).

Heterogeneity assessments showed no intertrial heterogeneity for the outcomes of gram-negative bacteremia (\( \chi^2 = 9.56; df = 9; P = .38 \)) and mortality (\( \chi^2 = 12.6; df = 9; P = .2 \)). Again, there was evidence for heterogeneity for the outcomes of gram-positive bacteremia (\( \chi^2 = 18.5; df = 9; P = .03 \)) and fever (\( \chi^2 = 20.0; df = 9; P = .03 \)), but the degree of heterogeneity was less extreme than that observed in the overall analysis.

For the second meta-analysis, we included the four trials comparing fluoroquinolones alone with fluoroquinolones plus fluoroquinolones. When the two studies [35, 36] that included oral nonabsorbable antibiotics (vancomycin, colistin, and an aminoglycoside) as a control regimen were removed, the results in terms of the clinical outcomes did not change significantly, but there was substantially less heterogeneity. The summary odds ratios for the outcomes were as follows: gram-negative bacteremia, 1.6 (95% CI, 0.6–4.3; \( P = .29 \)); gram-positive bacteremia, 0.59 (95% CI, 0.41–0.86; \( P = .005 \)); fever, 0.82 (95% CI, 0.6–1.1; \( P = .25 \)); and infection-related mortality, 1.09 (95% CI, 0.51–2.3; \( P = .8 \)). After the studies including control regimens were removed from the analysis, the heterogeneity tests yielded nonstatistically significant results for all the outcomes examined, including gram-positive bacteremia (\( \chi^2 = 4.6; df = 3; P = .19 \)).

Discussion

The goals of successful prophylaxis in neutropenic patients should include a reduction in the risk of developing specific infections and a reduction in infection-related mortality, a reduction in the number of episodes of febrile neutropenia, and a decrease in the empirical use of antibiotics for febrile episodes [1, 2].

Fluoroquinolones are now widely used as prophylaxis for bacterial infections in granulocytic patients. Several studies have shown that these drugs reduce the occurrence of gram-negative bacterial infections; however, the results in terms of other parameters of infection-related morbidity such as the overall incidence of bacterial infections and fever, the need for systemic antibiotics, and the occurrence of infection-related mortality are controversial [58, 59]. Fluoroquinolones provide poor coverage for streptococci and coagulase-negative staphylococci, which accounts for the increased incidence of alimentary tract colonization and subsequent risk of infection associated with their use [2, 58, 60]. Indeed, results from open or controlled studies showed a high rate of gram-positive bacteremia among granulocytic patients receiving prophylaxis with fluoroquinolones [5–9, 23, 24, 29]. Furthermore, the administration of fluoroquinolones has already been associated with the emergence and spread of resistant coagulase-negative staphylococci [61, 62].

These observations have prompted some investigators to evaluate the efficacy of adding gram-positive prophylaxis when fluoroquinolones are administered to granulocytic patients. Such studies have generally shown that combination prophylaxis reduces the incidence of infection due to gram-positive organisms, especially infections due to staphylococci; however, conflicting results in terms of the overall incidence of bacterial infections, episodes of fever, need for systemic antibiotics, and infection-related mortality have been obtained.

Continued debate thus surrounds the issue of the adequacy of fluoroquinolones for preventing bacterial infections in neutropenic patients [1, 2, 58, 59, 63–65]. Differences in study size, epidemiological circumstances, patient characteristics, and study design make the interpretation of the published results difficult. In this context, a meta-analysis of randomized studies (which provides a quantitative synthesis and a more-structured approach to evaluation of previous studies than does a traditional narrative review) can provide a means of answering important clinical questions that individual studies cannot answer definitively [66, 67].

In our study, we separately analyzed 13 randomized studies with fluoroquinolones alone (first meta-analysis) and six randomized studies with fluoroquinolones plus gram-positive prophylaxis (second meta-analysis). The meta-analytic techniques used, i.e., the fixed-effect model (Mantel-Haenszel method [46]) and the random-effect model (the method of DerSimonian and Laird [48]) differ because they are based on slightly different methods for weighting the sample size of individual trials. Both of these approaches represent well-standardized methods for weighting individual studies on the basis of their respective sample sizes.

Unfortunately, the same level of standardization has not yet been achieved in terms of quality scores for clinical trials. Indeed, there is presently no agreement as to how the results of these quality evaluations should be incorporated as weighting factors in the pooling process of a meta-analysis. As a result, the operative choice generally made by investigators performing meta-analyses is not based on the inclusion of these quality scores as weighting factors for mathematical algorithms. The results of these quality evaluations are therefore simply descriptive.

We felt justified in including randomized trials, regardless of design differences with respect to control regimens, since the evidence from previous comparative studies and one review [64] suggests that fluoroquinolones are uniformly more effective than control regimens, whether they consist of placebo, oral nonabsorbable antibiotics, or TMP-SMZ. That inclusion of these trials is justifiable was also confirmed by the results of our subgroup analysis of trials comparing fluoroquinolones with control regimens (oral nonabsorbable antibiotics or TMP-SMZ) as well as the results of three trials comparing fluoroquinolones with placebo (data not shown). In both cases,
group analysis did not result in a substantial change in the clinical outcomes observed in the overall analysis.

The four outcomes we evaluated were the occurrence of gram-negative bacteremia, the occurrence of gram-positive bacteremia, fever-related morbidity, and infection-related mortality. In agreement with the findings of previous randomized controlled trials, our findings from the first group of studies (combining results for 1,155 patients) demonstrated that the fluoroquinolones were more effective than control regimens (TMP-SMZ, oral nonabsorbable antibiotics, or placebo) for preventing gram-negative bacteremia in granulocytopenic patients (OR, 0.09; 95% CI, 0.05–0.16; \( P < .001 \)); this finding was statistically significant.

In contrast to the uncertain results of individual trials, the summary odds ratios in this meta-analysis showed no evidence of a significantly higher incidence of gram-positive bacteremia among patients treated with fluoroquinolones than among those who received control regimens (OR, 1.05; 95% CI, 0.76–1.45; \( P = .7 \)). For the outcome of fever, the summary odds ratio indicated a slight benefit for patients treated with fluoroquinolones over those treated with a control regimen, although this difference was not statistically significant (OR, 0.76; 95% CI, 0.56–1.04; \( P = .09 \)).

The second group of studies we examined included 957 patients in randomized studies that compared fluoroquinolones plus antimicrobial agents active against gram-positive microorganisms (penicillin G or penicillin V, vancomycin, or macrolide) with control regimens (fluoroquinolones alone [four studies] and oral nonabsorbable antibiotics [two studies]). The summary estimates calculated in this analysis suggest a difference in rates of gram-positive bacteremia that favored treatment with combined prophylaxis (OR, 0.46; 95% CI, 0.33–0.63; \( P < .001 \)); this finding is consistent with the results of individual studies [34–38, 40–43] that demonstrated a reduction in the incidence of gram-positive bacteremia, especially that due to streptococcal species, among patients receiving fluoroquinolones plus gram-positive prophylaxis. Our analysis revealed that a total of 28 null studies would be required to render the findings related to the outcome of gram-positive bacteremia nonsignificant.

The results of four studies of fluoroquinolones with or without gram-positive prophylaxis [39, 40, 42, 43] have shown a reduction in the incidence of bacteremia due to streptococcal species when gram-positive prophylaxis (penicillin G or penicillin V, amoxicillin, or oxithromycin) was added to a regimen of fluoroquinolones. In the two other trials [35, 36], the control group received oral vancomycin and a component of the prophylactic regimen that was not substantially less evidence of heterogeneity for both outcomes (\( P < .001–.03 \)). For the outcome of fever, the summary odds ratio indicates a similar efficacy for combined prophylaxis and control regimens (OR, 0.83; 95% CI, 0.62–1.13). By contrast, two (including the European Organization for Research and Treatment of Cancer trial [43]) of the six controlled studies with fluoroquinolones plus gram-positive prophylaxis [36] reported a significant reduction in fever-related morbidity.

In spite of these limited—but well documented—beneficial effects on some parameters of infection-related morbidity, neither fluoroquinolones alone nor fluoroquinolones plus gram-positive prophylaxis offered advantages over control regimens in reducing overall infection-related mortality. However, there were fewer deaths due to gram-positive infections among patients receiving prophylaxis with fluoroquinolones plus gram-positive coverage (1 of 18 deaths) than among patients receiving a control regimen (12 of 25 deaths). This difference reflects the reduced incidence of streptococcal bacteremia and the reduced number of deaths due to streptococcal infections and is consistent with findings from previous reports on the use of vancomycin, penicillin, macrolides, or rifampin as prophylaxis in this setting [34, 38, 41, 68–70].

Our quantification of heterogeneity showed that there was evidence of heterogeneity among the studies in terms of some of the outcomes examined (gram-positive bacteremia and fever in the first meta-analysis and gram-positive bacteremia in the second meta-analysis). Separate analysis of the potential source of this heterogeneity showed that study design played a major role. The exclusion of three trials with placebo groups from the first meta-analysis led to similar results in terms of overall odds ratios (i.e., gram-positive bacteremia, 1.05–1.13; fever, 0.76–0.72) and 95% confidence intervals, but there was substantially less evidence of heterogeneity for both outcomes (\( P < .001–.03 \)).

In the second meta-analysis, subgroup analysis after exclusion of two studies with control groups that received vancomycin as a component of the prophylactic regimen did not substantially change the overall odds ratios and 95% confidence intervals for the outcome of gram-positive bacteremia but rendered the degree of statistical heterogeneity nonsignificant.

In summary, the results of our meta-analyses suggest that prophylaxis with fluoroquinolones for bacterial infections in granulocytopenic patients reduces the incidence of gram-negative bacteremia among these patients, without increasing the incidence of gram-positive bacteremia; this benefit was not observed for patients who received control regimens. Moreover, the addition of gram-positive coverage to fluoroquinolone prophylaxis effectively reduced the overall incidence of gram-positive bacteremia, especially that due to streptococcal species.

Indeed, the problem of emergence of resistance is the principal drawback to prophylaxis with fluoroquinolones; the prophylactic administration of these drugs has been associated with the emergence and spread of resistant coagulase-negative staphylococci [61, 62]. In addition, failure of prophylaxis with fluoroquinolones...
has been reported during a waterborne epidemic of multiresistant *Pseudomonas aeruginosa* infection [24].

The issue of resistance to fluoroquinolones in gram-negative bacilli is of crucial importance, particularly for immuno compromised patients. It is of interest that in our analysis of randomized studies with fluoroquinolones, the statistical parameters (odds ratios and 95% confidence intervals) for the outcome of gram-negative bacteremia remained within a narrow range for all of the studies throughout the 8-year period (1986–1994). This finding is consistent with the observed continued efficacy of fluoroquinolones in suppressing gram-negative bacterial infections [12, 63]. However, as predicted by Pizzo [1], the concern about the long-lasting efficacy of fluoroquinolones in preventing gram-negative infections has been confirmed by recent reports of the emergence of fluoroquinolone-resistant *Escherichia coli* in neutropenic cancer patients in Europe [71–75].

Some aspects of these resistant strains need to be addressed. First, there is some evidence that both the emergence of newly resistant clones and the spread of specific clones among a group of patients can occur [65, 71, 74, 76]. It has been argued that the increase of resistance to fluoroquinolones might reflect an increasing dissemination of fluoroquinolone-resistant strains in the general population [65]. This increasing incidence of fluoroquinolone-resistant *E. coli* correlates well with the increasing use of these drugs in clinical practice, and it is conceivable that under such epidemiological circumstances, immunocompromised patients (especially those with previous exposure to fluoroquinolones) will continue to become colonized and be at risk of developing bloodstream infections due to fluoroquinolone-resistant strains [65, 74, 75].

Second, a substantial number of fluoroquinolone-resistant *E. coli* isolates from a cancer center showed cross-resistance to other antibacterial agents of unrelated classes such as TMP-SMZ, doxycycline, chloramphenicol, and β-lactams [71, 74, 75]. That is a potential risk of the development of cross-resistance to fluoroquinolones and unrelated drugs in *P. aeruginosa* and the Enterobacteriaceae after exposure to fluoroquinolones has been already reported [76–79]. These patterns of multidrug resistance were associated with changes in outer membrane proteins of these organisms.

On the other hand, there is some evidence that resistance to fluoroquinolones is associated with decreased pathogenicity in certain bacteria. Fluoroquinolone-resistant gram-negative mutants are characterized by prolonged doubling time, decreased viability under laboratory conditions, decreased mobility, and hypersusceptibility to human serum [74, 78, 80, 81]. It is therefore conceivable that such mutants are unlikely to cause systemic infections in the general population. However, in a population subset such as granulocytopenic patients, these mutants could overwhelm host defenses and cause bloodstream infections. This possibility threatens to undermine the long-term efficacy of prophylaxis with fluoroquinolones during episodes of granulocytopenia.

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### References


