Reappraisal With Meta-Analysis of the Addition of Gram-Positive Prophylaxis to Fluoroquinolone in Neutropenic Patients

By Mario Cruciani, Marina Malena, Oliviero Bosco, Stefano Nardi, Giovanni Serpelloni, and Carlo Mengoli

**Purpose:** Past reports and meta-analyses indicate that fluoroquinolones are highly effective in preventing Gram-negative infections in neutropenic cancer patients, but offer inadequate coverage for Gram-positive infections. We evaluated by meta-analysis the efficacy of the addition of antimicrobial agents with enhanced Gram-positive activity to prophylaxis with quinolones.

**Materials and Methods:** Randomized trials comparing fluoroquinolones alone (ciprofloxacin, ofloxacin, pefloxacin, or norfloxacin) with fluoroquinolone in combination with Gram-positive prophylaxis (rifampin, vancomycin, amoxicillin, raxithromycin, or penicillin) were retrieved. We pooled relative risks (RRs) using a fixed-effects model.

**Results:** Nine trials (1,202 patients) published between 1993 and 2000 meet inclusion criteria. Compared with fluoroquinolone alone, Gram-positive prophylaxis reduced total bacteremic episodes (RR, 1.54; 95% CI, 1.26 to 1.88), streptococcal infections (RR, 2.20; 95% CI, 1.44 to 3.37), coagulase-negative staphylococcal infections (RR, 1.46; 95% CI, 1.04 to 2.04), and rate of febrile patients (RR 1.08; 95% CI, 1.00 to 1.16). Occurrence of clinically documented infections, unexplained fever, and infectious mortality was similar in the two groups. The addition of Gram-positive prophylaxis, however, significantly increased side effects (RR, 0.46; 95% CI, 0.28 to 0.76). Rifampin use resulted in a higher incidence of undesirable effects.

**Conclusion:** Considering the lack of cut-clear benefit on some parameters of morbidity and mortality, routine use of Gram-positive prophylaxis is not advisable. This strategy, however, should be particularly valuable in subgroups of patients at high risk of streptococcal infection (eg, those with severe and prolonged neutropenia or mucositis, and those receiving cytarabine). Problems of tolerability and the potential for the emergence of resistant microorganisms should be considered when prescribing prophylaxis with enhanced Gram-positive activity to neutropenic patients.


**THE EFFICACY** of fluoroquinolones in preventing Gram-negative infection in neutropenic cancer patients is well documented.1-3 Conversely, the beneficial effects of fluoroquinolone prophylaxis on mortality and on other parameters of morbidity are debatable. Moreover, concerns about the long-lasting efficacy of fluoroquinolones in preventing Gram-negative infections became apparent after studies reporting the emergence of fluoroquinolone-resistant Gram-negative bacilli.4-6 Nevertheless, in those centers in which resistance has not emerged, prophylaxis with fluoroquinolones is still widely in use. Gram-positive organisms, predominantly viridans streptococci and coagulase-negative staphylococci, have emerged as the most commonly isolated pathogens responsible for infections among neutropenic patients receiving fluoroquinolones.7-10 This is not surprising, given that viridans streptococci and coagulase-negative staphylococci generally are resistant to fluoroquinolones, and use of these agents would select for colonization with these microorganisms. Early reports have found that the benefit of quinolone prophylaxis can be improved by adding agents with enhanced Gram-positive activity.11,12 Consequently, strategies to reduce Gram-positive infections by combining Gram-positive coverage with fluoroquinolone prophylaxis have been widely explored. A number of controlled clinical trials have evaluated the efficacy of prophylaxis with oral fluoroquinolone in combination with antimicrobial agents active against Gram-positive bacteria.9,13-26 Indeed, these studies are somewhat heterogeneous with regard to design, patient selection, antimicrobial agent used, and outcomes investigated. Moreover, the benefit of prophylaxis with enhanced Gram-positive coverage has been substantiated in some of these studies, whereas other studies failed to demonstrate consistent advantages.

In this study, we evaluated by systematic review and meta-analyses the randomized studies investigating the efficacy of the addition of antimicrobial agents with enhanced Gram-positive activity to a fluoroquinolone-based prophylactic regimen in neutropenic cancer patients.

**MATERIALS AND METHODS**

**Literature Search**

The medical literature was searched for relevant studies published between 1984 and October 2002. The search was carried out on Medline, CancerLit database, Database of Abstracts of Reviews of Effects, and on Cochrane Library. Medical subject heading terms used were neutropenia or agranulo-
cytosis and bacterial infections. The bibliographies from the articles retrieved were consulted to supplement the computer search. Where possible, we contacted the authors of publications for missing or incomplete information.

**Study Selection**

We included only randomized studies involving granulocytopenic patients receiving chemotherapy for cancer. We required that studies compared prophylactic regimens that were based on fluoroquinolone combined with drugs specifically acting against Gram-positive bacteria, with a control arm in which subjects were given fluoroquinolone alone.

**Outcome Measures**

We extracted data on bacteremic episodes, Gram-positive infections, Gram-negative infections, clinically documented infections, mortality, and side effects related to prophylaxis. Where possible, we also recorded data on febrile morbidity (first day of fever and rates of patients with fever and with unexplained fever).

**Quality Assessment**

We assessed the quality of each trial with two different methods. First, we assessed the methodology of each trial with a scale developed by Jadad et al.\(^\text{27}\) This scale evaluates the randomization and double blinding, and reports of dropouts and withdrawals. We also used a second quality scale to assess the trials for study design, data analysis, and presentation of results.\(^\text{1}\) This 15-category instrument included inclusion and exclusion criteria, number of patients excluded from the trial and the reasons for exclusion, definition of study drug and control regimen (drug, dose, timing, and duration), randomization and double blinding, prognostic factors among groups, definition of outcome measure, 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 CIs. The reviewers assigned value of 0 to 1.0 for each item (0, absent or cannot be determined; 0.5, partial; and 1.0, present). Each trial was independently scored by two of the authors (M.M. and O.B.) and any areas of disagreement were arbitrated by a third author (M.C.).

**Statistical Analysis**

A conventional meta-analysis was performed with the use of the Mantel-Haenszel fixed-effects model.\(^\text{28}\) The study-specific and the common 95% CIs were calculated by the method of Woolf.\(^\text{29}\) We used risk ratio (RR) as a measure of the effect size. The Der Simonian and Laird\(^\text{30}\) random effects model was applied only when the heterogeneity test produced a P value \(\leq .05\). Pooled rates were assessed to calculate the number of patients that needed to be treated to prevent one event.\(^\text{31}\)

Sensitivity analysis was performed to determine if quantitative results differed with the exclusion of individual studies.

**Assessment of Publication Bias**

Graphic funnel plots were generated to visually inspect for publication bias.\(^\text{32}\) The statistical methods for detecting funnel plot asymmetry were the regression asymmetry test of Egger et al\(^\text{33}\) and the rank correlation tests of Begg and Mazumdar.\(^\text{34}\) When there was evidence of an asymmetric funnel plot, we used the trim and measure of the effect size. The Der Simonian and Laird\(^\text{30}\) random effects model was calculated by the method of Woolf.\(^\text{29}\) We used risk ratio (RR) as a measure of the effect size. The Der Simonian and Laird\(^\text{30}\) random effects model was applied only when the heterogeneity test produced a P value \(\leq .05\). Pooled rates were assessed to calculate the number of patients that needed to be treated to prevent one event.\(^\text{31}\)

Sensitivity analysis was performed to determine if quantitative results differed with the exclusion of individual studies.

**Heterogeneity Assessment**

We assessed the heterogeneity of study results using the Cochran Q test.\(^\text{37}\)

**RESULTS**

We retrieved 2,269 articles dealing with neutropenia and bacterial infections. Fifteen comparative published trials of fluoroquinolones combined with Gram-positive prophylaxis were identified as being appropriate for inclusion in our analysis on the basis of the predetermined inclusion and exclusion criteria.\(^\text{13-26}\) Of these, four randomized studies were excluded because they compared fluoroquinolones combined with Gram-positive agents to oral nonabsorbable antibiotics,\(^\text{23,24}\) placebo,\(^\text{25}\) or no treatment.\(^\text{26}\) One study that evaluated ofloxacin plus rifampin was excluded because it was not randomized and included a historical control group receiving norfloxacin or no antibiotic prophylaxis.\(^\text{12}\) We also excluded another case-control study in which patients receiving quinolone alone were compared with matched patients receiving a quinolone plus penicillin.\(^\text{9}\)

The main characteristics of the nine randomized studies\(^\text{13-21}\) that met the inclusion criteria are shown in Table 1. All patients had severe and prolonged neutropenia related to intensive chemotherapy. Patients received oral ciprofloxacin (four studies), ofloxacin (two studies), pefloxacin (two studies), or norfloxacin (one study) with or without rifampin (three studies), vancomycin (two studies), amoxicillin (one study), roxithromycin (one study), or oral or intravenous penicillin (two studies). With the exception of duration of neutropenia in one study, there was no evidence of imbalance in patient baseline characteristics.
Thus, only episodes in the group receiving Gram-positive prophylaxis. 69 of 72 episodes in recipients of quinolones, and 46 of 48 febrile patients. Almost all of the episodes of staphylococcal for staphylococcal infections, and 1.08 (95% CI, 1.00 to 1.16) for total bacteremic episodes, 1.46 (95% CI, 1.04 to 2.04) for coagulase-negative staphylococcal bacteremia from total episodes of bacteremia after removal of coagulase-negative staphylococcal bacteremia were reported among 1,202 patients (0.4%).

The occurrence of clinical documented infections, Gram-negative infections, unexplained episodes of fever, and infectious mortality, was similar in the two groups (Table 2). The time of the onset of the first febrile episode was similar in the two groups (7.8 ± 2.9 days in fluoroquinolone recipients and 8.2 ± 4.1 days in Gram-positive prophylaxis recipients). Adding Gram-positive prophylaxis, however, significantly increased the occurrence of side effects (RR favoring fluoroquinolone alone, 0.46; 95% CI, 0.28 to 0.76). In the large majority of cases, adverse events and/or toxic reactions possibly or definitely related to study drugs consisted of gastrointestinal intolerance and/or abnormal liver function test. Untoward events severe enough to require discontinuation of prophylaxis were reported in two studies with rifampin (seven patients), in a study with roxithromycin (four patients, including one patient with hepatitis, renal failure, and lethal outcome after therapy with asparagus), and in a study with ciprofloxacin with or without amoxicillin (five patients, two in the ciprofloxacin arm).

In sensitivity analysis, after exclusion of two studies with rifampin and one study with roxithromycin as Gram-positive prophylaxis, the difference in the occurrence of side effects was no longer statistically significant. Exclusion of the study by Gomez-Martin et al yielded the largest change (RR, 0.66; 95% CI, 0.37 to 1.16).

For the other outcomes analyzed, the exclusion of any single study yielded only minimal change on the effect size and did not alter the effect of Gram-positive prophylaxis.

**Publication Bias Assessment**

Figures 3 and 4 represent Begg’s funnel plots that test for publication bias. Funnel plots for the outcomes total episodes of...
Fig 1. Pooled relative risk (RR) estimates and their 95% CIs for the following outcomes: total bacteremia (A), streptococcal infections (B), and staphylococcal infections (C). Studies are identified by first author (year of publication). Size of squares is proportional to Mantel-Haenszel weighted RR. EORTC, European Organization for Research and Treatment of Cancer.
Fig 2. Pooled relative risk estimates and their 95% CIs for the following outcomes: patients with fever (A), side effects (B), and mortality (C). Studies are identified by first author (year of publication). Size of squares is proportional to Mantel-Haenszel weighted RR. EORTC, European Organization for Research and Treatment of Cancer.

**A**

- Fanci (1993): Risk Ratio (95% CI) 0.96 (0.71 to 1.31), % Weight 6.1
- Kern (1994): Risk Ratio (95% CI) 1.30 (0.79 to 2.72), % Weight 13.2
- Broun (1994): Risk Ratio (95% CI) 0.98 (0.65 to 1.48), % Weight 4.4
- EORTC (1994): Risk Ratio (95% CI) 1.12 (1.02 to 1.24), % Weight 56.8
- Hidalgo (1997): Risk Ratio (95% CI) 1.00 (0.77 to 1.30), % Weight 5.1
- Gomez-Martín (2000): Risk Ratio (95% CI) 1.11 (0.94 to 1.30), % Weight 14.5
- Overall (95% CI): Risk Ratio (95% CI) 1.08 (1.00 to 1.16)

**B**

- Fanci (1993): Risk Ratio (95% CI) 0.70 (0.17 to 2.84), % Weight 9.1
- Kern (1994): Risk Ratio (95% CI) 0.19 (0.02 to 1.59), % Weight 11.3
- Broun (1994): Risk Ratio (95% CI) 1.05 (0.07 to 16.69), % Weight 2.2
- EORTC (1994): Risk Ratio (95% CI) 0.83 (0.37 to 1.90), % Weight 26.5
- Bow (1996): Risk Ratio (95% CI) 0.92 (0.06 to 14.17), % Weight 2.3
- Hidalgo (1997): Risk Ratio (95% CI) 0.14 (0.02 to 1.06), % Weight 15.5
- Ford (1998): Risk Ratio (95% CI) 1.05 (0.22 to 4.90), % Weight 6.5
- Gomez-Martín (2000): Risk Ratio (95% CI) 0.05 (0.01 to 0.61), % Weight 26.7
- Overall (95% CI): Risk Ratio (95% CI) 0.46 (0.28 to 0.76)

**C**

- Fanci (1993): Risk Ratio (95% CI) 0.48 (0.05 to 4.99), % Weight 9.6
- Kern (1994): Risk Ratio (95% CI) 0.64 (0.11 to 3.69), % Weight 14.5
- Broun (1994): Risk Ratio (95% CI) 2.10 (0.20 to 21.42), % Weight 4.6
- EORTC (1994): Risk Ratio (95% CI) 1.00 (0.44 to 2.27), % Weight 52.0
- Bow (1996): Risk Ratio (95% CI) 0.92 (0.14 to 6.19), % Weight 9.8
- Hidalgo (1997): Risk Ratio (95% CI) 1.00 (0.07 to 14.90), % Weight 4.7
- Ford (1998): Risk Ratio (95% CI) 1.05 (0.07 to 16.22), % Weight 4.6
- Overall (95% CI): Risk Ratio (95% CI) 0.94 (0.52 to 1.71)
bacteremia, streptococcal infections, fever, and side effects, as well as Begg-Mazudmar and Egger tests, supported the lack of evidence for publication bias. The robustness of some of these conclusions was also indicated by the calculation of the number of negative or null studies required to lead meta-analysis results to a level that was not statistically significant (29 for the outcome bacteremia and 19 for the outcome streptococcal infections).

For the outcome staphylococcal infection, the asymmetric appearance of the funnel plots and the Egger test \(P = .017\) suggest that publication bias may be present. After adjusting for missing studies using the trim and fill approach, the estimate RR changed from an original value favoring Gram-positive prophylaxis to a value that was not statistically significant (Fig 4). However, the correlation test of Begg and Mazudmar was not statistically significant, thus suggesting that asymmetry of funnel plots might be due to factors other than publication bias.

**Heterogeneity Assessment**

The results of heterogeneity assessment showed no intertrial heterogeneity for all of the outcomes analyzed.

### Table 2. Outcomes in Pooled Studies That Compared F and GPP for Prevention of Infection in Neutropenic Patients

<table>
<thead>
<tr>
<th>Type of Illness</th>
<th>Treatment</th>
<th>Pooled Rates</th>
<th>Relative Risk</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremic episodes</td>
<td>F</td>
<td>28.2</td>
<td>1.54</td>
<td>1.26 to 1.88</td>
<td>&lt; .0001</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>14.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcal infections</td>
<td>F</td>
<td>6.0</td>
<td>2.20</td>
<td>1.44 to 3.37</td>
<td>.0006</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>3.5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcal infections</td>
<td>F</td>
<td>9.8</td>
<td>1.46</td>
<td>1.04 to 2.04</td>
<td>.02</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>5.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative infections</td>
<td>F</td>
<td>4.3</td>
<td>1.00</td>
<td>0.56 to 1.80</td>
<td>NSS</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDI</td>
<td>F</td>
<td>8.8</td>
<td>0.89</td>
<td>0.64 to 1.24</td>
<td>NSS</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>11.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile patients</td>
<td>F</td>
<td>79.5</td>
<td>1.08</td>
<td>1.00 to 1.16</td>
<td>.03</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>72.4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained fever</td>
<td>F</td>
<td>43.4</td>
<td>1.04</td>
<td>0.88 to 1.23</td>
<td>NSS</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>35.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>F</td>
<td>3.8</td>
<td>0.94</td>
<td>0.52 to 1.71</td>
<td>NSS</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>F</td>
<td>2.9</td>
<td>0.46</td>
<td>0.28 to 0.76</td>
<td>.003</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>5.7</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3. Number of Patients That Needed to Be Treated, Percent Reduction of Risk, and Publication Bias Assessment**

<table>
<thead>
<tr>
<th>Type of Illness</th>
<th>Treatment</th>
<th>No./Total</th>
<th>Crude Rates</th>
<th>% Risk Reduction</th>
<th>95% CI*</th>
<th>NNT</th>
<th>PBA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremic episodes</td>
<td>F</td>
<td>169/595</td>
<td>28.4</td>
<td>11.1</td>
<td>6.2 to 16.4</td>
<td>9.0</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>108/587</td>
<td>18.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptococcal infections</td>
<td>F</td>
<td>63/595</td>
<td>10.5</td>
<td>5.6</td>
<td>2.1 to 10.6</td>
<td>17.7</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>28/587</td>
<td>4.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcal infections</td>
<td>F</td>
<td>72/595</td>
<td>12.1</td>
<td>4.4</td>
<td>0.9 to 9.0</td>
<td>22.8</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>48/587</td>
<td>8.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative infections</td>
<td>F</td>
<td>26/595</td>
<td>4.3</td>
<td>0.0</td>
<td>2.9 to 1.7</td>
<td></td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>48/587</td>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDI</td>
<td>F</td>
<td>58/530</td>
<td>10.9</td>
<td>1.2</td>
<td>2.7 to 4.2</td>
<td>80.6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>64/525</td>
<td>12.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Febrile patients</td>
<td>F</td>
<td>363/462</td>
<td>78.5</td>
<td>6.7</td>
<td>4.1 to 9.2</td>
<td>14.8</td>
<td>2</td>
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<tr>
<td></td>
<td>GPP</td>
<td>33/464</td>
<td>71.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unexplained fever</td>
<td>F</td>
<td>176/404</td>
<td>43.5</td>
<td>7.2</td>
<td>2.0 to 12.6</td>
<td>13.8</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>165/457</td>
<td>36.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>F</td>
<td>20/491</td>
<td>4.0</td>
<td>0.2</td>
<td>3.0 to 2.0</td>
<td>562.6</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>21/496</td>
<td>4.2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Side effects</td>
<td>F</td>
<td>21/549</td>
<td>3.8</td>
<td>4.3</td>
<td>1.8 to 5.9</td>
<td>23.3</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>GPP</td>
<td>45/544</td>
<td>8.2</td>
<td></td>
<td></td>
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</tbody>
</table>

**Abbreviations:** NNT, number of patients that needed to be treated to prevent one event; PBA, publication bias assessment on the basis of calculations of the minimum number of negative (null) studies required to lead the results of the meta-analysis to a statistically nonsignificant level; F, fluoroquinolone alone; GPP, fluoroquinolone + gram-positive prophylaxis; CDI, clinically documented infections.

*Calculated on the basis of the crude rate in the control group (baseline risk) and pooled rate in the treatment group.

†95.8% of total episodes were sustained by coagulase-negative staphylococci.
DISCUSSION

A continuous debate surrounds the issue of the adequacy of fluoroquinolones in preventing bacterial infections in neutropenic patients. Without a doubt, prophylaxis with fluoroquinolones has led to a decrease in the occurrence of Gram-negative infections in neutropenic patients. When quinolones are used as prophylaxis, the rate of Gram-negative bacteremia is reduced to 1% to 2%.38 Three meta-analyses of clinical trials examining the benefit of fluoroquinolone prophylaxis in neutropenic patients have been published.1-3 Since that time, however, there has been a continuous interest in the use of quinolone prophylaxis, and a number of trials investigating the efficacy of fluoroquinolones alone or in combination with Gram-positive prophylaxis have been carried out.

One of the drawbacks to prophylaxis with fluoroquinolones is represented by the emergence of resistant strains. Reports of fluoroquinolone-resistant Escherichia coli causing bacteremia among cancer patients are a matter of concern.4-6

Given that prophylaxis with fluoroquinolones has, until now, led to a remarkable reduction in the occurrence of Gram-negative infections during neutropenia in many centers, gener-
studies have shown a benefit of the addition of Gram-positive prophylaxis to fluoroquinolone prophylaxis (ciprofloxacin, ofloxacin, pefloxacin, or norfloxacin) to fluoroquinolone prophylaxis (ciprofloxacin, ofloxacin, pefloxacin, or norfloxacin) was evident on some parameters of infectious morbidity, but not on mortality. Our quantification of heterogeneity showed no intertrial heterogeneity for the outcomes analyzed.

Compared with patients who received fluoroquinolone alone, patients who received Gram-positive prophylaxis experienced 11.1% fewer bacteremic episodes (from 29.5% to 18.4%), as a result of a decrease in streptococcal and coagulase-negative staphylococcal infections. There also was limited evidence for a reduction of febrile morbidity in patients receiving prophylaxis with fluoroquinolones. This reduction translated into decreases of 6.7% (from 78.5 to 71.7%) in the number of febrile patients, but the unexplained episodes of fever and the first day of fever were comparable between groups. Moreover, there was no significant effect of the addition of Gram-positive prophylaxis to quinolone in terms of infectious mortality (RR, 0.95; 95% CI, 0.53 to 1.71). On the contrary, side effects were significantly less common among recipients of fluoroquinolone alone than among patients receiving fluoroquinolone combined with Gram-positive prophylaxis (RR, 0.46; 95% CI, 0.28 to 0.76; P = .003). In sensitivity analysis, however, the effects of rifampin (two studies) and macrolide (one study) on side effects were marked:

After exclusion of these single studies, the pooled RR was no longer statistically significant.14,18,20

Publication bias is a significant threat to the validity of meta-analysis. In this meta-analysis, evidence of publication bias with graphic and statistical methods was not detectable for the outcomes overall bacteremia, streptococcal infections, rates of febrile patients, unexplained episodes of fever, and side effects. Evidence also existed for the robustness of some of these conclusions. For the outcome staphylococcal infections, there was evidence of publication bias with the regression asymmetry test of Egger et al.32 This was not confirmed when the rank correlation test was applied.33 Moreover, the results of the Begg and Mazumdar test were consistent for all of the end points analyzed. Thus, a false-positive test for bias with the former test cannot be excluded.

Quality assessment is of absolute relevance to systematic reviews.22 Methodologic problems with trials involving neutropenic patients have been reported.59 These observations have prompted the Immunocompromised Host Society and, more recently, the Immunocompromised Host Society in conjunction with the Multinational Associations for Supportive Care in Cancer, to produce a set of guidelines on methodologic issues for clinical trials in neutropenic patients.60,61

On average, the quality of the studies included in this analysis was not ideal. Many studies did not pay attention to statistical issues, such as calculation of CIs and estimation of study power. Among the nine studies included in this analysis, five described methods of randomization and two were blinded. Generally, however, there was uniformity in patient selection criteria, settings, definition of outcomes assessed, and characteristics of the patients included in the trials.
 Clinicians will have to decide whether fluoroquinolone prophylaxis of bacterial infections is still worthwhile in neutropenic patients with cancer. The efficacy of quinolone prophylaxis in preventing Gram-negative infections has ultimately emerged in recent reports from European cancer centers, and shows a striking rebound of Gram-negative bacteremias after discontinuation of prophylaxis with fluoroquinolones. Data from Switzerland show an increase of the proportion of Gram-negative bacteremias from 25% to 85% of all bloodstream infections. However, the shift was recorded concomitantly with a decrease of Gram-positive bacteremias.

Our data confirm the continuous efficacy of quinolone prophylaxis in preventing Gram-negative infection. The pooled incidence of Gram-negative infection was approximately 4% in both groups.

*Staphylococcus aureus* was isolated from blood in a negligible proportion (0.4%) of patients. In contrast, coagulase-negative staphylococci were by far the leading cause of bacteremia, with 135 episodes reported among 1,202 patients (11.2%). Given that the increase in coagulase-negative staphylococci bacteremia is related strictly to the increasing use of indwelling intravenous catheters, strategies aimed at an optimal management of intravascular devices, including insertion and maintenance, should prevent these infections more efficiently than the use of systemic antibiotic prophylaxis.

Straightforward conclusions from the results of this meta-analysis, however, are not easy to reach. Overall, the results of our meta-analysis do not support the routine use of Gram-positive coverage in combination with quinolone prophylaxis in neutropenic patients. Considering the lack of clear benefit in terms of some parameters of morbidity and mortality, it probably makes sense to use Gram-positive coverage in particular subgroups of neutropenic patients. We found that prophylaxis with enhanced Gram-positive coverage is uniformly effective in reducing streptococcal infections. Risk factors for streptococcal infection that have been identified include severe neutropenia, oral mucositis, bone marrow transplantation, and administration of high-dose cytarabine. According to these observations, such a prophylactic strategy should be of particular efficacy in neutropenic patients at high risk of streptococcal infection. In contrast, prophylaxis should be avoided in those patients for whom neutropenia is expected to be short and mucositis uncommon (eg, solid tumor patients or patients with certain lymphomas). Problems with tolerability should be taken into account when prescribing prophylaxis. As our meta-analysis supports, rifampin use could result in higher incidence of undesirable effects. Oral vancomycin and penicillin have been found to be at least as effective as rifampin but are better tolerated, and should be preferred in this setting. In this case, however, the potential for the emergence of penicillin-resistant streptococci and vancomycin-resistant enterococci has to be monitored strictly and weighed against the benefits of treatment.

**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

The authors indicated no potential conflicts of interest.

**REFERENCES**


guidelines of the Immunocompromised Host Society/Multinational Association for Supportive Care in Cancer, with emphasis on outpatient studies. Clin Infect Dis 35:1463-1468, 2002


