Counterpoint: Routine Anti-Bacterial Prophylaxis Is Not Indicated in Neutropenic Patients With Hematological Malignancies

Michael Kleinberg, MD, PhD, Baltimore, Maryland

Infections are a leading non-oncologic cause of death and morbidity in neutropenic cancer patients, particularly in patients with leukemia or high-grade lymphomas and in bone marrow or stem cell transplant recipients. The universal practice of early empiric treatment of suspected bacterial infections in neutropenic patients with potent antibiotics was introduced almost 30 years ago and has been widely credited with dramatically reducing infectious mortality in patients with leukemia. Patients with prolonged neutropenia, especially granulocyte counts less than 100/mcL, are at greatest risk for adverse outcomes, including death. Neutropenic fever heralds potentially serious infection and, therefore, is considered the appropriate trigger for starting empiric antibacterial therapy even in the absence of positive culture results. Virtually all patients with leukemia require empiric antibacterial treatment for suspected infections at some time during neutropenia. Prophylaxis differs from empiric therapy in that prophylactic antibacterials are given to the as yet uninfected neutropenic patient before the patient reaches the period of highest infectious risk. The potential benefit of prophylaxis is further reduction in infectious mortality and morbidity over and above that attained with empiric treatment alone by preventing bacterial infections in the first place.

Despite this straightforward logic, prophylaxis of bacterial infections in neutropenic patients remains a controversial issue, even though multiple studies have been published over the past 25 years. A noticeable decrease can be seen in the numbers of papers published over the past 5 years on antibacterial prophylaxis in neutropenia. Prophylaxis differs from empiric therapy in that prophylactic antibacterials are given to the as yet uninfected neutropenic patient before the patient reaches the period of highest infectious risk. The potential benefit of prophylaxis is further reduction in infectious mortality and morbidity over and above that attained with empiric treatment alone by preventing bacterial infections in the first place.
to their neutropenic patients. Others believe that universal antibacterial prophylaxis has little impact on neutropenic patient outcomes. The purpose of this article is to explore some of the unresolved critical issues surrounding prophylaxis and bacterial infections in neutropenic patients.

Prophylaxis can be given with antibacterials that are systemically distributed after gastrointestinal absorption (such as sulfa compounds, most quinolones) or with nonabsorbable agents confined to the gastrointestinal tract (aminoglycosides, norfloxacin) for selective gut decontamination. In theory, prophylaxis eradicates nascent microinfections before they become clinically apparent, reduces colonization of pathogens leading to decreased incidence of bacterial infections, delays onset of first fever in febrile neutropenia, decreases use of parenteral empiric antibacterials, and improves survival. In theory, reduction by prophylaxis of the number of bacterial infections associated with first neutropenic fever leads to fewer fatal empiric antibacterial failures. From the clinical point of view, the potential beneficial impact of prophylaxis on patient outcomes is tied directly to the effectiveness of empiric antibacterial therapy.

Clinical trials of prophylaxis show consistently reduced colonization and reduction of superficial and invasive bacterial infections (including bacteremias) when compared with placebo in neutropenic patients.2–7 The extent of reduction depends on the spectrum and potencies of the prophylactic agents. Newer broader spectrum quinolones such as ofloxacin/levofloxacin decrease bacteremias with both gram-positive and gram-negative bacteria versus placebo. In comparison, ciprofloxacin and norfloxacin are less potent against gram-positive bacteria.6 Greater reductions in gram-positive bacteremias can be achieved by adding another antibacterial, such as rifampin, to ofloxacin.6,8

My intent is not to exhaustively review the trial literature comparing fluoroquinolone, or fluoroquinolone with another agent to augment anti-gram-positive activity, with either placebo or non-quinolone antibacterial agents. Rather, examination of two meta-analysis studies is instructive.8,9 Cruciani et al.1 published a meta-analysis of randomized, comparative fluoroquinolone prophylaxis trials performed from 1984 to 1994. Thirteen studies compared results for 619 patients randomized to receive fluoroquinolone prophylaxis alone versus 536 patients receiving comparators. Placebo was the comparator in three of these 13 trials (104 receiving fluoroquinolone vs. 111 in control arm), and other antibacterials (primarily trimethoprim-sulfamethoxazole) were the controls in the 10 other trials. In an analysis of pooled data from all 13 trials, fluoroquinolone prophylaxis significantly reduced incidence of gram-negative bacteremia (odds ratio [OR], 0.09; 95% confidence interval [CI], 0.05–0.16; P < .001) compared with controls. No significant differences were found between fluoroquinolone and control regimens in incidence of gram-positive bacteremias or neutropenic fevers.

Engels et al.7 published a second meta-analysis of randomized trials reported from 1966 to 1996, which included many of the same studies in the Cruciani meta-analysis.1 In nine studies, fluoroquinolones (364 patients) were compared with placebo or with nonabsorbable antifungal agents (367 patients). Fluoroquinolone (343 patients) was compared with trimethoprim-sulfamethoxazole (334 patients) prophylaxis in nine other studies. In an analysis of pooled data from the nine placebo and nonabsorbable antifungals trials, fluoroquinolones significantly reduced the incidence of gram-negative bacterial infections (OR, 0.21; 95% CI, 0.11–0.37) and gram-negative bacteremias (OR, 0.23; 95% CI, 0.11–0.49; P < .001). Reduced incidence of fevers (OR, 0.85; 95% CI, 0.73–0.99) was seen in analysis of all 18 studies. However, fever reduction with fluoroquinolone prophylaxis was not seen when blinded trials were analyzed separately. No significant difference was found between fluoroquinolone prophylaxis and control regimens in incidence of gram-positive bacteremias (OR, 0.21; 95% CI, 0.36–1.32).

One would expect that reduced rates of bacteremia in patients receiving prophylaxis compared with placebo should translate into decreased infectious morbidity and mortality, at least from gram-negative bacteremias. All things considered, it is preferable not to be bacteremic. Unexpectedly (to many), the Cruciani and Engels meta-analysis studies1,2 failed to demonstrate statistically significant survival or morbidity benefits for patients receiving fluoroquinolone prophylaxis versus control comparators. Cruciani et al.1 found no significant difference in infection-related mortality in patients receiving fluoroquinolones versus control regimens (OR, 0.79; 95% CI, 0.47–1.34 and OR, 1.03; 95% CI, 0.43–1.63, based on meta-analysis by two statistical models that differed in weighting individual studies). Engels et al.7 also found no
survival benefit with fluoroquinolone versus placebo or nonabsorbable antifungal prophylaxis (OR, 1.04; 95% CI, 0.40–2.70 for 5 studies suitable for analysis). The wide CIs are attributable, in part, to the low mortality rates in all the trials included in the two meta-analyses. Crude infectious mortality rates in the Cruciani study were 4.6% and 5.4% for fluoroquinolone versus control-treated (placebo, trimethoprim-sulfamethoxazole, nonabsorbable antifungals) patients, a difference in infection-related mortality of less than 1%. Corresponding crude infectious mortality rates in the Engels meta-analysis were 5.1% and 5.5% for fluoroquinolone versus control (placebo, trimethoprim-sulfamethoxazole, nonabsorbable antifungals) patients.

The three blinded, placebo-controlled trials\textsuperscript{9–11} in the Cruciani and Engels meta-analyses\textsuperscript{5,7} are typical of other prophylaxis trials reported in the literature. One trial enrolled only 26 patients and is not discussed further.\textsuperscript{9} Another study was performed at a single cancer center, enrolling 68 patients with leukemia over 14 months in 1984 and 1985 who developed neutropenia with a mean duration of 32 days.\textsuperscript{10} Thirty-five patients were randomized to receive norfloxacin and 33 patients received placebo. Three patients taking norfloxacin developed gram-negative bacteremias, and 12 patients receiving placebo experienced gram-negative bacteremias. Two patients in each arm died of bacterial infections with crude rates for bacterial infection-related mortality of 6% in both the norfloxacin and placebo arms. Three of the four deaths were caused by \textit{Pseudomonas aeruginosa}, a bacterium that may not have been particularly responsive to the ticarcillin/gentamicin/vancomycin empiric regimen. The third study was conducted in the early 1990s and involved 119 randomized leukemic patients at eight centers. Of the patients, 62 received enoxacin and 57 received placebo.\textsuperscript{11} Empiric treatment was with amnoglycoside plus either an antipseudomonal penicillin or third-generation cephalosporin. Only one gram-negative bacteremia was seen in the enoxacin-treated patients, but 14 were noted in the placebo arm. However, only five deaths occurred (2 caused by fungal infections, 1 by progressive leukemia, 1 by unspecified infection, and 1 undetermined). These latter two studies show how timely empiric antibacterial therapy can treat placebo-treated patients despite increased numbers of gram-negative bacteremias compared with fluoroquinolone treatment.

A closer look at the prospective prophylaxis versus placebo trial design illustrates why improved clinical outcomes were not seen with fluoroquinolone prophylaxis. Patients, usually patients with leukemia, bone marrow or stem cell transplant recipients, and others with expected prolonged neutropenia, were randomized or similarly allocated to receive antibiotic prophylaxis or placebo (no prophylaxis). Endpoints such as days before first fever, colonization with particular pathogens, reduction in need for intravenous antibiotics, reduction in superficial and invasive bacterial infections associated with first neutropenic fevers, are all attributable entirely or in large part to the efficacy of fluoroquinolone prophylaxis. Conversely, comparisons of clinical outcomes such as infectious mortality, differences in hospitalization lengths of stay, and other morbidity measures are not solely dependent on receiving prophylaxis or placebo.

These clinical outcomes depend also on the success or failure of the empiric antibacterial regimen initiated with neutropenic fever. For patients receiving prophylactic fluoroquinolones, successful clinical outcomes depend on prophylaxis-related reduction in incidence of bacterial infections followed by effective empiric parenteral antibacterial treatment for those neutropenic patients who develop fevers subsequently (including patients with bacterial infections that breakthrough prophylaxis). For patients given placebo (or no prophylaxis), successful outcomes depend entirely on the effectiveness of empiric parenteral antibacterials for neutropenic fevers. To further complicate the analysis, overall infection-related mortality and morbidity outcomes depend not just on the initial empiric antibacterial regimen, but also on subsequent modifications (such as adding vancomycin or antifungal) to the initial empiric regimen. Therefore, the most unambiguous measure of clinical effectiveness of fluoroquinolone prophylaxis is mortality and morbidity attributable to infections associated with first neutropenic fever. Mortality and morbidity associated with late breakthrough infections by fungal, viral, and resistant bacterial pathogens are more representative of empiric anti-infective regimen failures.

It is instructive to consider four hypothetical limiting conditions. First, suppose that prophylaxis is no better than placebo in reducing infection-related mortality and morbidity. Therefore, whether empiric antibacterial therapy is either poorly or highly effective...
makes no difference in the mortality or morbidity endpoints for patients receiving prophylaxis versus placebo. Outcomes depend entirely on the effectiveness of empiric antibacterial therapy. Now, consider that prophylaxis is superior to placebo. If empiric therapy is highly effective, patients receiving either prophylaxis or placebo will have low mortality and morbidity rates. In fact, the potential effectiveness of prophylaxis becomes irrelevant as the effectiveness of empiric antibacterial treatment in preventing death and morbidity attributable to bacterial infections approaches 100%. Paradoxically, the greatest impact of effective prophylaxis would be seen in the setting of poorly active empiric therapy. By preventing bacterial infections in the first place, fewer neutropenic patients receiving prophylaxis, compared with placebo, would have serious bacterial infections with their neutropenic fevers for whom poorly active empiric therapy would then fail.

The effectiveness of empiric antibacterial therapy with its subsequent modifications can be seen in several randomized prospective studies in which patients did not receive quinolone prophylaxis. For example, the French Cefepime Study Group compared cefepime plus amikacin with ceftazidime plus amikacin as initial empiric therapy for febrile neutropenic patients. Patients with hematologic malignancies comprised 95% of patients, and 40% of patients were bone marrow transplant recipients. Sixty-five percent of patients received antibacterial prophylaxis, which was limited to gut decontamination with nonabsorbable agents. A total of only 3 infectious deaths occurred of 114 bacterial isolates in the 319 treated neutropenic patients (mortality rate, 1%). Peacock et al. compared ciprofloxacin plus piperacillin with amikacin plus piperacillin as empiric therapy in 471 neutropenic patients (76% hematologic malignancies) with fever. Enrolled patients did not receive quinolone prophylaxis. Only 3 patients (<1% of neutropenic patients) died from their initial bacterial infections (109 patients with bacteremias). Cometta et al. reported on a large EORTC trial where neutropenic patients were treated with either piperacillin-tazobactam plus amikacin or ceftazidime plus amikacin. Only 115 of the 806 enrolled patients were given quinolone prophylaxis. There were only 7 deaths (of 181 bacteremias) attributable to failure of the initial empiric antibacterials. Similar low mortality rates were seen in ceftazidime versus combination antibiotics and clinafoxacin versus imipenem trials for febrile neutropenic patients when no prophylactic quinolones were given within 7 days of study entry.

The studies described in the preceding paragraph, spanning almost 2 decades of investigation, are characteristic of multiple comparative trials that show the success of early empiric antibacterial therapy in reducing mortality associated with initial fevers in febrile neutropenic patients to 1% or less. The very effectiveness of empiric antibacterial therapy in febrile neutropenia overshadows potential benefits of fluoroquinolone prophylaxis. Assume for the sake of discussion that reduction in bacteremias with fluoroquinolone prophylaxis in neutropenic patients translates into a decrease in mortality of 50% compared with placebo. Given the success rates of empiric antibacterial regimens, this assumed 50% reduction with prophylaxis would lead to decreases in mortality from approximately 1% to 0.5% for all patients with febrile neutropenia (the intent-to-treat population) and from about 2% – 4% to 1% – 2% in the subset of neutropenic patients with bacteremias for placebo versus prophylaxis, respectively. It is this miniscule potential mortality benefit, not the lack of statistical significance, which is the most noteworthy result from the Cruciani and Engels meta-analysis studies.

A large prospective, randomized, placebo-controlled trial would be required to test, once and for all, whether fluoroquinolone prophylaxis reduces infectious mortality and morbidity. It would be a daunting task to design and complete successfully this trial to prove that such a potentially small reduction in mortality with fluoroquinolone prophylaxis was statistically significant. Thousands of evaluable patients would be required at prohibitive costs. Moreover, a trial powered to discriminate 1% to 2% differences in outcome would be highly prone to confounding from multiple causes. Extensive entry stratifications would be necessary to equalize distributions of patient variables between fluoroquinolone and placebo arms. Variables such as underlying diagnosis; age; induction, consolidation, or relapse disease status; interinstitutional clinical practices; among others could all confound trial outcomes if unequally distributed to even small degrees. Any of a number of uncontrollable factors may be unequally distributed by chance despite randomization. For these reasons, this “mother of all prophylaxis trials” is unlikely to ever be conducted.
Even if fluoroquinolone is statistically proven to decrease bacterial infectious mortality in febrile neutropenia, would a 1% to 2% reduction in mortality be medically significant? Each life “saved” with fluoroquinolone would require exposing 100 to 200 neutropenic patients, who receive no benefit from prophylaxis, to potential adverse side effects. The relatively low costs and excellent safety profiles of oral fluoroquinolones present minimal expense and risk. Conversely, adverse outcomes caused by infections with bacteria resistant to multiple antibacterials are a critical downside risk with widespread prophylaxis of oncologic patients.

Resistance to antimicrobials is encoded by genes inserted into chromosomal DNA or onto extrachromosomal transmissible plasmids. Bacteria may carry a dozen or more antimicrobial resistance genes on a single large mobile element. In practical terms, this means that fluoroquinolones have the potential for at-once selection of bacteria resistant not only to quinolones, but also simultaneously to β-lactams, aminoglycosides, and other classes of antibacterials. In the nightmare scenario, fluoroquinolone prophylaxis leads to colonization replacement of sensitive commensal bacteria by multidrug-resistant bacteria. These resistant bacteria then cross the mucosal-skin barrier disrupted by chemotherapy and infect the neutropenic patient. A potential disaster can occur if (1) resistant bacteria are not killed by empiric antibacterials started with first neutropenic fever; (2) resistant bacteria are virulent; or (3) modifications to original empiric antibacterial agents are delayed until culture and antibacterial sensitivity data are available.

Prophylaxis exerts selective pressure that preferentially promotes colonization with and amplification of resistant bacteria. The association with antibacterial prophylaxis and potential dangers posed by infections with resistant bacteria has been reviewed extensively. Problems with antibacterial resistance are local; problems arise in individual hospitals even individual wards. Clinicians in different cities, states, and countries caring for neutropenic patients will not witness the same incidences of adverse events, including excess deaths potentially associated with resistant bacteria and prophylaxis. Excess mortality and morbidity caused by resistant bacteria are rarely captured in clinical trials of empiric therapy in patients with febrile neutropenia, because patterns of antibacterial resistance also fluctuate with time, not just geography. The impact of bacterial resistance was seen in one febrile neutropenia trial in which lower than expected success rates were reported because the initial empiric antibacterials were modified prematurely by clinicians for fear of infection with resistant bacteria that were epidemic in the participating hospitals. In fact, fluoroquinolone prophylaxis should not be given to patients with high likelihoods of colonization with resistant bacteria.

Estimating rates of excess prophylaxis-attributable mortality resulting from infections with resistant bacteria is very difficult for individual institutions. However, an excess mortality rate of 0.5% because of resistant bacterial infections would essentially negate the benefit from fluoroquinolone prophylaxis, assuming that benefit even exists. In a medium-sized cancer center, this may represent one excess death per year by particularly worrisome pathogens such as MRSA, penicillin-resistant viridans streptococci, and β-lactamase-producing gram-negative bacteria (including Pseudomonas species). A hematologist sharing attending clinician responsibilities on a leukemia or bone marrow transplant unit would be unlikely to appreciate this low incidence of excess deaths from resistant bacterial infections. Even if it was noticed, proving that an individual adverse outcome from resistant bacterial infections was causally related to prophylaxis would still be impossible. Therefore, the potentially deleterious effects of fluoroquinolone prophylaxis will probably be missed, except during clonal outbreaks caused by resistant bacteria.

Conclusions

Struggles in defining the appropriate role for antibacterial prophylaxis in cancer patients are actually a testament to the extraordinary success of empiric approaches to suspected bacterial infections in neutropenic patients. The majority of leukemia patients and marrow transplant recipients simply will not benefit from routine antibacterial prophylaxis, even if prophylaxis is ultimately proven to reduce mortality and morbidity. Is there any role for antibacterial prophylaxis in at risk neutropenic patients if a mortality benefit has not been shown in any clinical trials? The answer to this question requires reformulating the central question. Instead of asking whether antibacterial prophylaxis is beneficial given to all neutropenic
patients, we should be asking which subset of neutropenic patients at highest risk of adverse infectious outcomes would be most likely to have decreased mortality and morbidity with fluoroquinolone prophylaxis. For example, a mortality or morbidity benefit has not been shown for fluconazole prophylaxis given broadly to patients with hematologic malignancies to prevent fungal infections.\(^\text{27,28}\) However, 3 prospective randomized, comparative trials showed that fluconazole prophylaxis decreased mortality from invasive candidiasis in allogeneic transplant recipients, but not in leukemias or autologous transplant recipients.\(^\text{29–31}\) There may indeed exist similar patients with hematologic malignancies who would benefit from fluoroquinolone prophylaxis. We just do not yet know who these patients are.

## References


