Fluoroquinolone Prophylaxis in Patients with Neutropenia

Stephen H. Zinner
Mount Auburn Hospital, Cambridge, and Harvard Medical School, Boston, Massachusetts

(See the article by Reuter et al. on pages 1087–93)

Since the early report, by Karp et al. [1], of the beneficial effects of norfloxacin on the incidence of bacteremia and other bacterial infections in patients with neutropenia and cancer, the use of fluoroquinolones as prophylactic agents has been controversial. The results of 2 meta-analyses more or less agreed that these antibiotics reduced the incidence of gram-negative rod bacteremia, as well as episodes of fever [2, 3]. However, no study has truly demonstrated a definitive benefit with regard to infection-related mortality or, for that matter, to the outcome of treatment of the underlying malignancy.

During the past 15 years, the use of fluoroquinolones to prevent infections in patients with neutropenia has varied in different parts of the world. The past 2 versions of the Infectious Diseases Society of America guidelines for the use of antimicrobial agents for patients with neutropenia and cancer failed to recommend these (or other antibacterial) agents for routine use in the prevention of bacterial infections [4, 5]. However, many European cancer centers have used these agents routinely, and this has been credited with reducing the frequency of gram-negative rod bacteremia and contributing to the shift toward gram-positive cocal bacteremia that had been recognized 10–15 years ago, although gram-negative bacteria have reemerged more recently [6, 7]. Well-documented evidence of significant increases in fluoroquinolone resistance among Escherichia coli strains has been published by researchers at many health care centers in Europe, including by a group in Ulm, Germany, who present an interesting and challenging article in this issue of Clinical Infectious Diseases [8].

Reuter et al. [8] present the results of a study that was intended to monitor the effects of fluoroquinolone prophylaxis on morbidity and antibiotic resistance during 3 periods of 1 year each. The study was shortened during the second phase, after only 3 weeks of discontinuation of fluoroquinolone prophylaxis, because of the occurrence of a dramatic increase in mortality that was attributed to gram-negative rod bacteremia. During the 3 weeks after the prophylactic use of levofloxacin was discontinued, 4 (44.4%) of 9 patients experienced an episode of gram-negative rod bacteremia, compared with only 15 (4.8%) of 310 patients during the preceding year of fluoroquinolone use. Three of the 4 cases of bacteremia were caused by E. coli, and all 4 organisms isolated were susceptible to the fluoroquinolone, whereas most of the isolates from cases of bacteremia were fluoroquinolone resistant during the preceding period of fluoroquinolone prophylactic treatment. The rate of gram-negative rod bacteremia dropped to former levels when fluoroquinolone prophylaxis was reintroduced. Moreover, infection-related mortality increased from 1% to 33.3% and then decreased to 1.4% over the 3 periods. Thus, this study is probably the first to suggest that fluoroquinolone prophylaxis has a significant impact on infection-related mortality.

Several unanswered questions are raised by these intriguing but limited data. Why does fluoroquinolone prophylaxis still reduce rates of gram-negative rod bacteremia in the same health care centers that report rises in fluoroquinolone resistance among gram-negative bacterial isolates? What is the possible mechanism for the continued “clinical prophylactic efficacy” of fluoroquinolone prophylaxis in the face of dramatically rising resistance to these drugs? Why was the rate of gram-negative rod bacteremia observed during the 3 weeks without fluoroquinolone prophylaxis higher than that reported by most institutions that do not use fluoroquinolone prophylaxis? Why did the rate of gram-positive bacteremia increase during the period when fluoroquinolone prophylaxis was stopped, which was contrary to expectations and concerns raised by others who worried that fluoroquinolone use would increase these rates? [9, 10]. Reuter et al. [8] correctly question whether fluoroquinolone-resistant bacteria are more virulent, but, unfortunately, this suggestion could not be addressed definitively in their article.

Reuter et al. [8] would like to generalize...
their results. As much as I would like to concur with this desire (especially since replication of the study is unlikely), I am not sure that generalization from these results can be justified, primarily owing to the following 2 concerns. First, only 9 patients were observed during the 3-week period that demonstrated their findings. Second, were these 9 patients somehow different from those in the larger group observed during the first year? The 310 neutropenic episodes observed in the first study year occurred in a group that included a mixture of patients with high-risk conditions (leukemia or lymphoma) and lower-risk conditions (solid tumor, aplastic anemia, or amyloidosis). Were all or most of the 9 patients observed during the discontinuation period at high risk? This suggestion is supported by the much higher rates of transfer to the intensive care unit and of polymicrobial infection during the 3 weeks of discontinuation of fluoroquinolone prophylaxis. In addition, the very rapid occurrence of these infections after discontinuation of prophylactic treatment is hard to explain.

The entire issue of fluoroquinolone prophylaxis for patients with neutropenia and cancer leads to the question of the efficacy of outpatient oral therapy for fever in low-risk patients [11, 12]. The Ulm group’s finding of high rates of infection and colonization with fluoroquinolone-resistant gram-negative rods [8, 13] raises concern about the future efficacy of oral fluoroquinolone regimens in this population.

As William Hazlitt wrote in 1830, “When a thing ceases to be a subject of controversy, it ceases to be a subject of interest” [14]. The current study by Reuter et al. [8] supports the continuing interest in defining optimal methods for minimizing or preventing serious bacterial infections in patients with neutropenia and cancer.

**Acknowledgments**

**Potential conflicts of interest**. S.H.Z. has received recent research funding from Aventis Pharmaceuticals, Bayer, Cubist Pharmaceuticals, Pfizer, and Theravance; has served as a consultant for Abbott Pharmaceuticals, Advancis Pharmaceuticals, AstraZeneca, Aventis Pharmaceuticals, Bayer, Cubist Pharmaceuticals, Oscent, Pfizer, Theravance, Vicuron Pharmaceuticals, Wyeth-Ayerst Laboratories, and Zynx Health; and is also a member of the speakers’ bureaus for AstraZeneca, Aventis Pharmaceuticals, Bayer, Bristol-Myers Squibb, Pfizer, and Wyeth-Ayerst Laboratories.

**References**