Original Article

Antibacterial Prophylaxis in Patients with Neutropenia

Brahm H. Segal, MD,[a] and Alison G. Freifeld, MD,[b] *Buffalo, New York, and Omaha, Nebraska*

Key Words

Neutropenia, quinolone, TMP-STX, fever, prophylaxis, empirical therapy

Abstract

Patients with cancer and chemotherapy-induced neutropenia are at risk for severe bacterial infections. This risk is not uniform among all cancer patients but is dependent primarily on the depth and duration of neutropenia and the type of underlying disease. Accordingly, the decision whether to use antibacterial prophylaxis to prevent serious infections in these patients requires a balance between expected benefit and the risks for infection, adverse drug-related events, and emergence of antibiotic resistance. Although antibacterial prophylaxis has the potential to benefit all patients with chemotherapy-induced neutropenia, the benefit regarding reduction in documented infections has been firmly established only in patients with neutropenia expected to exceed 7 days. A recent meta-analysis showed enhanced survival in patients receiving antibacterial prophylaxis during neutropenia; most patients enrolled in the analyzed trials had a hematologic malignancy. Among patients with neutropenia at lower risk for infectious complications (a category that includes most patients with solid tumor malignancies), the main benefit of antibacterial prophylaxis relates to a reduction in fever rather than documented infections. The authors advise quinolone prophylaxis (levofloxacin is preferred), in patients with an expected duration of neutropenia (absolute neutrophil count < 1000/μL) of more than 7 days. Trimethoprim-sulfamethoxazole should be used in patients at risk for *Pneumocystis jiroveci* (formerly *P carinii*), such as childhood acute lymphoblastic leukemia. In patients with neutropenia expected to last 7 days or less and not receiving immunosuppressive regimens (e.g., systemic corticosteroids), the authors recommend no initial prophylaxis. However, if such patients develop fever during neutropenia, they should be considered for outpatient empiric therapy with an oral quinolone–containing regimen if they meet criteria for low risk for complications. (*JNCCN* 2007;5;235–242)

From the [a]Division of Infectious Diseases, Roswell Park Cancer Institute, Buffalo, New York, and [b]Immunocompromised Host Infectious Diseases Program, University of Nebraska Medical Center, Omaha, Nebraska.

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Correspondence: Brahm H. Segal, MD, Division of Infectious Diseases, Roswell Park Cancer Institute, Elm and Carlton Streets, Buffalo, NY 14263. E-mail: brahm.segal@roswellpark.org

Bacterial infections are common complications of antineoplastic cytotoxic chemotherapy and may be life-threatening. The risk factors for developing a serious bacterial infection are largely related to the depth and duration of neutropenia. Afebrile patients with absolute neutrophil counts (ANC) of less than 500/μL are at the highest risk for the development of fever that may signify a bacterial infection. This risk increases as the ANC falls below 100/μL and as the duration of neutropenia lengthens.[1] The rate of fever or documented infection (neutropenic fever of unknown origin is sometimes equated with suspected infection) ranges from less than 10% among patients undergoing intermittent cytotoxic therapy for solid tumors or lymphoma with less than 5 days of severe neutropenia,[2–5] to 75% to 100% among patients undergoing hematopoietic stem cell transplantation (HSCT) and those with acute leukemia undergoing intensive cytotoxic chemotherapy.[1,6]

In a secondary analysis of patients enrolled in trials of empirical antibacterial therapy for neutropenic fever, the dominant risk factor for bacteremia was the duration of neutropenia.[7] Neutropenia lasting 1 to 5 days before trial entry was associated with a relative risk for bacteremia of 5.2 compared with no neutropenia; neutropenia of 6 to 15 days had a relative risk of 7.35. Patients with a hematologic disease and those undergoing HSCT were also more likely to have bacteremia than were patients with solid tumors. This difference likely relates to a shorter duration of neutropenia and less mucosal toxicity in regimens used for most solid tumors compared with hematologic malignancies and HSCT. Chemotherapy-related oral and gastrointestinal mucositis play an especially im-

portant role in contributing to increased infection risk factors among neutropenic patients by predisposing them to blood stream infections by viridans group streptococcal bacteremia,[8–10] gram-negative rods,[11] and *Candida* species.[12] Additional factors that may increase risk for infections include use of indwelling catheters, instrumentation (e.g., endoscopy) and surgery, severe periodontal disease, malnutrition, steroid use, and comorbidities such as renal and hepatic insufficiency.

Early efforts to reduce the incidence of serious bacterial infections involved the routine use of antipseudomonal beta-lactam agents as empirical antibacterial therapy at the onset of neutropenic fever. This approach significantly reduced mortality associated with bacterial infections and remains standard care, allowing for the development of increasingly potent cytotoxic regimens over the years.[13]

Although in the 1960s and 1970s, gram-negative bacterial pathogens (Enterobacteriaceae and *Pseudomonas aeruginosa*) were the principal causes of bacteremia, gram-positive bacterial infections have become predominant, with approximately two thirds of nosocomial bloodstream infections in patients with hematologic malignancies being gram-positive.[14–16] This shift toward infection by gram-positive organisms likely reflects the widespread use of implantable venous catheters, more effective agents against gram-negative pathogens, and more common use of antibacterial prophylaxis. Despite the increased frequency of gram-positive relative to gram-negative infections, the principles of initial management of neutropenic fever have remained relatively constant, with an emphasis on the use of antibiotics that are bactericidal against gram-negative bacteria. The use of vancomycin should be tailored to specific circumstances, such as catheter-associated infections and bacteremia by gram-positive pathogens.

Strategies for Prevention and Early Treatment of Bacterial Infections

Three general strategies for preventing and treating infections include 1) prophylaxis; 2) empirical therapy; and 3) treatment of established infections. In the prophylactic mode, antibiotics are administered during a prespecified high-risk period (e.g., neutropenia) in an effort to prevent infections. Empirical therapy involves administering antibiotics at the onset of neutropenic fever with the rationale of treating a possible occult infection. In most cases of undifferentiated neutropenic fever of unknown origin, an infectious origin is not identified. Table 1 summarizes premises that are at the foundation of prophylactic and early treatment strategies for serious infections in highly immunocompromised patients.

Prophylactic antibiotics to prevent the onset of fever and infection in neutropenic patients have been studied extensively since the 1970s. Although the Infectious Diseases Society of America (IDSA) guidelines on management of neutropenic fever recognize the evidence that antibacterial prophylaxis in high-risk neutropenic patients reduces the frequency of Gram negative infections, the IDSA advises against prophylaxis.[17] This recommendation is based on the concern for emergence of antibiotic-resistant bacteria and a review of previous studies that showed lack of a survival benefit associated with antibacterial prophylaxis, despite decreases in gram-negative bacterial infections. Similarly, guidelines from the American Society for Blood and Marrow Transplantation, Centers for Disease Control, and Infectious Diseases Society of America;[18] the Infectious Diseases Working Party of the German Society of Hematology and Oncology;[19] the Sociedad Chilena de Infectologia; and the Japan Febrile Neutropenia Study Group[20] have not recommended the routine application of antibacterial chemoprophylaxis strategies.

Table 1 Premises for Prophylactic and Early Treatment Strategies for Bacterial Infection in Patients with Cancer and Chemotherapy-Induced Neutropenia

Premises
1) The more dangerous the infection (e.g., gram-negative rod sepsis), the greater the need for effective prophylaxis. Conversely, prophylaxis is not warranted for infections that are not serious or do not respond easily to therapy.
2) The higher the incidence of infection within a given population, the more likely clinicians are to use prophylaxis.
3) The safer the antimicrobial agent, the more likely clinicians are to use it in a large number of patients (e.g., as prophylaxis) in which only a minority would be expected to benefit but very few would incur toxicity.
4) The potential early benefit of prophylaxis to an individual patient must be balanced by the risk for subsequent selection of resistant pathogens in that individual, within a given hospital, and the larger community.

The NCCN Fever and Neutropenia Clinical Practice Guidelines in Oncology have adopted a more permissive position regarding antibacterial prophylaxis. If antibacterial prophylaxis (generally with a quinolone) is used, the NCCN Fever and Neutropenia Panel recommended that it be limited to patients expected to experience profound neutropenia (fewer than 100 neutrophils per microliter) for more than 7 days.[21] This recommendation was rated category 2B, defined as nonuniform consensus (but no major disagreement), based on lower-level evidence, including clinical experience, that the recommendation is appropriate. Prophylactic antibiotics are definitively not recommended by the panel for patients with short-term neutropenia, anticipated to last less than 7 days.

Recent published studies have provided additional insight into the benefits and limitations of prophylaxis among neutropenic patients with varying degrees of risk for serious infectious complications.[5,22,23] These results shift the benefit versus risk analysis to favor prophylaxis in patients with neutropenia lasting more than 7 days. Although prophylaxis may prevent neutropenic fever in a small proportion of lower-risk patients, a strong counterpoint is the potential danger that selecting for resistant pathogens may outweigh this small benefit if prophylaxis of low-risk patients were widely adopted.

Agents Used in Antibacterial Prophylaxis

The choice of agents for antibacterial chemoprophylaxis has evolved over the past several decades. Reflecting that the bowel was a major portal of entry for gram-negative bloodstream infections, a variety of nonabsorbable antibiotic regimens, including oral vancomycin, gentamicin, and polymyxins, have been used in early studies of prophylaxis.[24,25] The value of nonabsorbable antibiotics is difficult to assess because of the small number of patients enrolled in trials, the use of historical controls, the variability of oral regimens studied, and the use of oral antibiotics together with other infection prevention strategies, such as mucosal antiseptic agents.[26] In addition, these regimens were poorly tolerated and are no longer used in common practice. Today, antibacterial prophylaxis in adults with neutropenia principally involves quinolones; trimethoprim-sulfamethoxazole (TMP-STX) is used in specific patients at risk for *Pneumocystis jiroveci* (formerly *P carinii*) infection. *P. jiroveci* infection is almost never encountered in patients rendered neutropenic by cytotoxic agents in the absence of additional immunosuppressive agents, such as high-dose corticosteroids.

TMP-STX

In an early study of TMP-STX as prophylaxis against *P. jiroveci* in children with acute lymphocytic leukemia, Hughes et al.[27] showed that this regimen had an additional benefit in protecting against bacterial infections and sepsis during neutropenia. Subsequent studies comparing TMP-STX with placebo have yielded inconsistent results, primarily showing modest treatment effects on reduction of febrile neutropenic episodes, clinically documented infections, and microbiologically documented infections, but not for all-cause mortality or gram-negative bloodstream infections.[28]

Several studies have shown that TMP-STX is less effective than quinolones in protecting against gram-negative infections.[28–31] Other disadvantages of TMP-STX prophylaxis include lack of activity against *P. aeruginosa*, hypersensitivity reactions, and potential for marrow suppression. Delay in myeloid recovery was associated with TMP-STX prophylaxis in some studies.[29–32]

TMP-STX provides effective prophylaxis against *P. jiroveci*. Although *P. jiroveci* is rarely associated with isolated neutropenia, comorbid conditions such as AIDS and treatment with regimens containing high-dose corticosteroids predispose patients to infection with this organism, and thus warrant TMP-STX prophylaxis.[33–35] The authors suggest that prophylaxis with TMP-STX be reserved for specific groups at high risk for becoming infected with *P. jiroveci*, such as those with childhood acute lymphoblastic leukemia, but not used as routine antibacterial prophylaxis in adult patients with neutropenia. Specific patients who warrant prophylaxis against *P. jiroveci* are described in the NCCN Fever and Neutropenia Guidelines.[21] Because of the potential concern about quinolone-induced arthropathy in children, several centers use TMP-STX as prophylaxis during neutropenia in children.

Quinolones

Quinolones are the most commonly used prophylactic antibacterial agents in adults with chemotherapy-induced neutropenia. A meta-analysis of trials of quinolone prophylaxis in neutropenic patients showed a clear benefit in reducing aerobic gram-negative rod

infections.[31] Engels et al.[31] evaluated 18 trials with 1408 patients in which quinolones were compared with either placebo or TMP-STX. Patients who received quinolones had approximately 80% fewer gram-negative infections than those who did not, leading to an overall reduction in total infections. The reduction in fever was small and not significant in blinded trials. Quinolone prophylaxis did not affect mortality in this meta-analysis.

Although the frequency of quinolone-resistant gram-negative isolates was not significantly affected by quinolone prophylaxis in this meta-analysis,[31] individual studies have reported resistance problems occurring in the setting of broad quinolone prophylaxis. Quinolone-resistant *Escherichia coli, P. aeruginosa*,[36,37] and *Stenotrophomonas maltophilia*[38] have been associated with quinolone prophylaxis in some series. Gomez et al.[39] evaluated the clinical and microbiologic outcomes of patients with leukemia and febrile neutropenia during a period in which ciprofloxacin prophylaxis was used and a subsequent period in which quinolone prophylaxis was abandoned because of a high prevalence of quinolone-resistant Enterobacteriaceae. No differences were seen between the cohorts with respect to bacteremia rates or significant complications, but quinolone-resistant *E. coli* was higher in the group that received prophylaxis. Martino et al.[40] reported that discontinuation of a policy of norfloxacin prophylaxis in an inpatient oncology ward was associated with a significant increase in the rate of fluoroquinolone-susceptible enterobacterial bloodstream infections, but no difference in the incidence of febrile neutropenia, fever of unknown origin, or bacteremia during the first febrile episode.

The rate of gram-positive infections and fungal infections was not significantly affected by quinolone prophylaxis in this meta-analysis.[31] This is an important consideration given the occurrence of an increased rate of gram-positive infections in some prophylaxis trials using ciprofloxacin,[9,30] which has notoriously poor gram-positive activity. Viridans group streptococcal bacteremia breakthroughs have been associated with ciprofloxacin prophylaxis, an important consideration given the high incidence of morbidity and mortality associated with this pathogen in neutropenic patients.[41]

Combination prophylactic regimens have been used to overcome the inadequate activity of older quinolones against gram-positive bacteria. One large randomized study showed that adding penicillin to a quinolone (pefloxacin) reduced the rate of bacteremia (especially when caused by streptococcal species) compared with the quinolone alone.[42] Another randomized study showed that the combination of prophylactic ofloxacin and rifampin led to a reduction in gram-positive infections compared with ofloxacin alone.[43] Addition of these agents to quinolone prophylaxis, of course, defeats the concept of selective decontamination. A meta-analysis showed that adding gram-positive prophylaxis reduced total bacteremic episodes because it decreased streptococcal and coagulase-negative staphylococcal infections.[44] However, combination regimens were associated with increased side effects and did not affect the frequency of undifferentiated neutropenic fever, total documented infections, or infectious mortality.

Reevaluation of Fluoroquinolone Prophylaxis for Neutropenia

Review of the literature suggests that fluoroquinolones are the most useful and least toxic agents for bacterial prophylaxis in patients with neutropenia. However, the dilemma remains as to which patients would benefit the most from prophylaxis without incurring the problems of drug toxicity and resistance. Recently, another meta-analysis and 2 large randomized studies provided data to help guide this decision.

Gafter-Gvili et al.[23] conducted a meta-analysis of 95 randomized, controlled trials comparing antibiotic prophylaxis with placebo or no intervention or another antibiotic in afebrile patients with neutropenia. In this meta-analysis, unlike results from prior individual studies, antibiotic prophylaxis significantly decreased the risk for death when compared with placebo or no treatment. The survival benefit was more substantial when the analysis was limited to quinolones. Quinolone prophylaxis reduced the risk for all-cause and infection-related mortality, fever, clinically documented infections, and microbiologically documented infections.

This analysis had several limitations. Most trials involved hospitalized patients with hematologic malignancies, and data were inadequate to assess the relationship between duration and degree of neutropenia and relative risk for mortality. Data on all-cause mortality were available for only 40 of the 50 trials that compared antibiotic prophylaxis with placebo or no

treatment. Some of the larger trials did not report mortality. All of the individual studies included in the all-cause mortality analysis enrolled fewer than 100 patients per treatment arm, and thus were not powered individually to detect a survival benefit of prophylaxis.

In addition, trials of prespecified high methodologic quality (e.g., double-blinded) yielded smaller effect estimates of prophylaxis than those of lower quality. No significant increase occurred in quinolone-resistant bacterial infections, although the length of observation may have been too short to detect the emergence of resistant bacteria. Despite these important limitations, the overall survival benefit of prophylaxis in patients with hematologic malignancies outweighs detriments related to adverse effects and development of resistance. However, the data from this analysis are inadequate to address any potential benefit of prophylaxis in patients with solid tumors who generally have shorter durations of neutropenia and are at a lesser risk for infectious complications.

Two recent large, randomized, placebo-controlled studies showed the benefit of levofloxacin prophylaxis in groups of patients with neutropenia who had different levels of risk for infectious complications during neutropenia.[5,22] Levofloxacin has similar activity against gram-negative pathogens compared with ciprofloxacin and ofloxacin, but has improved activity against certain gram-positive pathogens, including streptococci. Bucaneve et al.[22] evaluated levofloxacin prophylaxis in adult patients with cancer in whom chemotherapy-induced neutropenia (< 1000 neutrophils per microliter) was expected to occur for more than 7 days. This protocol intentionally excluded patients anticipated to have a short duration of neutropenia who would generally be candidates for outpatient management of neutropenic fever. Compared with placebo recipients, levofloxacin recipients experienced a lower rate of microbiologically documented infections, bacteremias, and single-agent gram-negative bacteremias. However, mortality was similar in the groups, with or without prophylaxis. The effects of prophylaxis were similar between patients with acute leukemia and those with solid tumors or lymphoma who were also treated with intensive cytotoxic chemotherapy. Cullen et al.[5] evaluated levofloxacin prophylaxis after chemotherapy for solid tumors and lymphomas. The primary outcome was the incidence of clinically documented febrile episodes (temperature > 38°C) attributed to infection. Secondary outcomes included the incidence of all probable infections, severe infections, and hospitalization. A total of 1565 patients underwent randomization, 87% with solid tumors and 13% with lymphoma. During the entire chemotherapy course, 10.8% of levofloxacin recipients had at least one febrile episode compared with 15.2% of placebo recipients (P = .01). Thus, using the primary end point of prevention of neutropenic fever 1000 hypothetical patients would have to receive prophylaxis during each cycle of chemotherapy-induced neutropenia to benefit only 44 patients. Hospitalization was required for treating infection (suspected and documented) in 15.7% of patients in the levofloxacin group and 21.6% of patients in the placebo group (P = .004). The incidences of severe infections, infection-related mortality, and overall mortality were similar in both groups.

Thus, the main advantage of levofloxacin prophylaxis in intermediate and higher-risk patients with chemotherapy-induced neutropenia (i.e., those with neutropenia anticipated to last more than 7 days) was a reduction in clinically significant bacterial infections, including gram-negative rod bacteremia. In contrast, the main advantage of prophylaxis in lower-risk patients with neutropenia was a small but statistically significant reduction in fever and hospitalization for neutropenic fever.[5] Reducing the incidence of significant infections may be a more clinically meaningful end point than reducing the incidence of neutropenic fever. Neither study conducted a systematic long-term evaluation of antimicrobial resistance.

An important consideration for low-risk patients with short durations of neutropenia is whether quinolone prophylaxis is of greater benefit than the option of outpatient quinolone treatment for fever and neutropenia, should it occur. Both the NCCN[21] and IDSA[17] recommend oral quinolone-based regimens as outpatient empirical therapy for neutropenic fever in adults meeting criteria for low risk for complications. Use of quinolone prophylaxis may preclude later use of these regimens as empirical therapy for neutropenic fever in the same patient. Guidelines on outpatient management of adults with neutropenic fever assume that quinolones were not used as prophylaxis; no evidence-based criteria guide the selection of oral antibiotics as empirical therapy for neutropenic fever

in cases of fever developing while receiving a prophylactic quinolone. Quinolone prophylaxis could ultimately result in a higher frequency of hospitalization and intravenous antibiotics in patients who would otherwise be candidates for outpatient management. In the study by Cullen et al.,[5] the modest difference in rates of hospitalization for suspected infection in patients treated with levofloxacin compared with those treated with placebo (15.7% vs. 21.6%, respectively) may be offset by exclusion of outpatient oral empirical therapy in patients receiving quinolone prophylaxis.

Another concern regarding quinolone prophylaxis relates to the potential overuse of vancomycin. Although controversial, some centers may use vancomycin as initial empirical therapy for neutropenic fever in patients receiving quinolone prophylaxis, because quinolones provide effective protection against gram-negative infections and increase the relative likelihood of a gram-positive infection as the cause of fever.[45] However, increased vancomycin use raises substantial concern about selection for vancomycin-resistant enterococci and *Staphylococcus aureus*.[46–48] The recent link between quinolone use and severe *Clostridium difficile* infections provides an additional cautionary note regarding excess use of quinolones.[49–51]

Faced with the choice of early (prophylactic) versus later (empirical therapy) initiation of antibiotics, the authors suggest that later administration may be a better approach for quinolone use in patients at lower risk for neutropenia.[52,53]

Conclusions

Prevention of infectious complications of neutropenia is a major goal in caring for patients undergoing cytotoxic antineoplastic therapy. The decision to use antibacterial prophylaxis and the selection of the specific agent require a balance between expected benefit and risk. Risk is determined based on immediate adverse effects of the drug (e.g., rash, gastrointestinal intolerance), the potential for selection for resistant pathogens that can harm the individual receiving prophylaxis, and the risk for introducing resistant organisms to a specific population of patients (e.g., those being treated at a cancer center). Early use of antibiotics as prophylaxis necessarily entails greater antibiotic exposure than targeting patients with early suspected infection (empirical therapy). The authors argue that the trial by Bucaneve et al.[22] and the meta-analysis by Gafter-Gvili et al.[23] shift the balance of the benefit/risk relationship in favor of quinolone prophylaxis in patients at high and intermediate risk for serious bacterial infections. However, in patients at lower risk for neutropenia who are expected to experience brief durations of neutropenia (which applies to most patients with solid tumors), the authors suggest that the modest benefit of levofloxacin prophylaxis may be outweighed by the risk of its widespread use. Even large, multicenter, randomized trials are not designed to effectively monitor for the emergence of antibiotic resistance, because these changes may take years to develop and occur sporadically in some centers but not others.[37] The risk for widespread quinolone prophylaxis leading to selection of antimicrobial-resistant pathogens cannot be overstated.[54]

Recently, the volume of fluoroquinolone use in hospitals was correlated with incidence of methicillin-resistant *S. aureus* (MRSA), and fluoroquinolone-resistant *E. coli* and *P. aeruginosa*.[55,56] The authors believe that the emergence of these increasingly lethal and difficult-to-treat pathogens requires that fluoroquinolone prophylaxis is consciously limited to only patients in whom substantial clinical benefit, in terms of significant decreases in serious morbidity, can be anticipated.

The authors advise quinolone prophylaxis (levofloxacin preferred) in patients with expected duration of neutropenia (absolute neutrophil count < 1000 per microliter) of more than 7 days. TMP-STX should be used in specific patients at high risk for *P. jiroveci*. In patients with neutropenia expected to last 7 days or less and not being treated with immunosuppressive regimens (e.g., systemic corticosteroids), the authors suggest administering no initial prophylaxis and reserving levofloxacin for outpatient empirical therapy for neutropenic fever in those who meet specific criteria for low risk for complications.

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