The Role of Quinolones as Prophylaxis in Neutropenic Patients

Neutropenia resulting from antineoplastic regimens is the major risk factor for infectious complications in patients with cancer. Patients with cancer and neutropenia have different levels of risk for infectious diseases. The degree and duration of neutropenia, presence of mucositis, immune impairment resulting from the underlying malignancy, and additional co-morbidities all influence the risk for infectious complications. Although evaluated in randomized trials over decades, antibacterial prophylaxis in patients with chemotherapy-induced neutropenia remains controversial. Antibacterial prophylaxis can reduce the incidence of Gram-negative infections and fever in neutropenic patients, and one meta-analysis showed a survival benefit of antibacterial prophylaxis. Quinolones are probably the most commonly used prophylactic agent in adults with chemotherapy-induced neutropenia. Based on concerns about selecting for antibiotic-resistant bacteria, antibacterial prophylaxis is generally restricted to neutropenic patients at high risk of infectious complications, such as those with neutropenia expected to last at least 7 days. This review will address the benefits and risks associated with quinolone prophylaxis in neutropenic patients.

Neutropenia and risk of infectious complications
It has been appreciated for 50 years that neutropenia predisposes patients to infectious diseases. The degree and duration of neutropenia predict the risk of infectious complications, and resolution of infections is linked to myeloid recovery (1). Chemotherapy-related oral and gastrointestinal mucositis play an important role in contributing to the increased risk of infection among neutropenic patients, predisposing to blood stream infections by α-hemolytic streptococci spp. (2–4), Gram-negative rods (5), and Candida spp. (6). Additional factors that can increase the risk of infectious complications include the use of indwelling venous catheters, use of systemic steroids and other immunosuppressive agents, and co-morbidities such as malnutrition and renal and hepatic impairment.

Whereas in the 1960s and 1970s, Gram-negative bacterial pathogens (coliforms and Pseudomonas aeruginosa) were the principal causes of bacteraemia, Gram-positive bacterial infections have since become predominant, with approximately two-thirds of nosocomial bloodstream infections in patients with hematological malignancies being Gram-positive (7–9). 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.

Efforts to reduce the incidence of serious bacterial infections involved the routine use of anti-pseudomonal β-lactam agents as empirical antibacterial therapy at the onset of neutropenic fever (10). Empirical antimicrobial therapy, by definition, denotes therapy for suspected, but not documented, infection. With improvements in antibacterial therapy and the rapid initiation of broad-spectrum antibiotic treatment at the onset of neutropenic fever, mortality from bacterial infections during chemotherapy-induced neutropenia became less common. Indeed, among patients with prolonged neutropenia (e.g., patients receiving induction or re-induction regimens for acute myelogenous leukemia), invasive fungal diseases equaled or exceeded bacterial infections as the predominant causes of infectious-related mortality at several centers (11). Thus, the question is raised regarding the expected benefits versus limitations...
of antibacterial prophylaxis for chemotherapy-induced neutropenia.

Strategies for prevention and early treatment of bacterial infections

Three general strategies for preventing and treating infections include: (i) prophylaxis; (ii) empirical therapy; and (iii) treatment of established infections (12). The prophylactic approach involves administering antibiotics in the absence of infection as a preventative strategy. Empirical antibiotic therapy means initiating antibiotics as therapy for neutropenic fever in the absence of a documented source. In contrast, therapy for an established infection is initiated after diagnosed (e.g., bacteremia) or presumed (e.g., pulmonary infiltrate) infection.

The selection of which strategy to implement is guided by a number of principles. The prophylaxis mode is likely to be used in patient groups in which the frequency and severity of a given infection is high. For example, Gram-negative bacterial sepsis is clearly an infection that can be life-threatening; whether to use a prophylactic agent will depend on the expected incidence of this complication without prophylaxis. Additional criteria for antibacterial prophylaxis relates to the safety and efficacy of the specific agent. For example, among antifungal agents, amphotericin B deoxycholate may be an effective agent, but its use as prophylaxis would be limited by toxicity. A third criterion relates to the use of early screening approaches to risk-stratify patients for a given complication. For example, the strategy of monitoring for cytomegalovirus (CMV) reactivation (by antigenemia or polymerase chain reaction [PCR]) as a trigger for pre-emptive anti-CMV therapy in transplant recipients is an attractive alternative to anti-CMV prophylaxis, which entails exposing a large group of patients to potentially toxic agents. Unfortunately, we do not have similar antigen-based or molecular tools to risk-stratify patients for bacterial infections.

Prophylactic antibiotics to prevent the onset of fever and infection in neutropenic patients have been studied extensively since the 1970s. More recently 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 (13, 14). These results likely shift the benefit/risk analysis in favor of prophylaxis in patients with neutropenia at intermediate or high risk of infectious complications.

Quinolone prophylaxis during neutropenia

Quinolones are the most commonly used prophylactic antibacterial agents in adults with chemotherapy-induced neutropenia. Of the quinolones, ciprofloxacin, ofloxacin, and levofloxacin have been the most extensively evaluated as prophylaxis in patients with cancer and neutropenia. Ciprofloxacin was more effective than norfloxacin in a randomized trial of neutropenic patients with hematological malignancies (15). These quinolones have similar broad spectrum activity against aerobic Gram-negative rods, but levofloxacin has broader coverage against certain Gram-positive organisms, such as Streptococcus pneumoniae.

The major benefits of prophylactic antibiotics are decreased Gram-negative infections and neutropenic fever. A meta-analysis of trials of quinolone prophylaxis in neutropenic patients showed a clear benefit in reducing aerobic Gram-negative rod infections (16). Engels et al. (16) evaluated 18 trials with 1,408 patients in which quinolones were compared with either placebo or trimethoprim-sulfamethoxazole (TMP-SMX). Patients who received quinolones had 80% fewer Gram-negative infections than those without prophylaxis, leading to an overall reduction in total infections. The reduction in fever was small, and in blinded trials, was not significant. Quinolone prophylaxis did not affect mortality in this meta-analysis. Another meta-analysis showed that prophylactic antibiotics during neutropenia were associated with a reduction in bacterial infection-related mortality (17).

Gafter-Gvili et al. (18) conducted a meta-analysis of 95 randomized, controlled trials comparing antibiotic prophylaxis with placebo or no intervention or another antibiotic in afebrile neutropenic patients. Antibiotic prophylaxis significantly decreased the risk of 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 of all-cause mortality as well as infection-related mortality, fever, clinically documented infections, and microbiologically documented infections. However, the authors noted several limitations of this analysis. Most of the trials involved hospitalized patients with hematological malignancies, and data were inadequate to assess the relationship between the duration and degree of neutropenia and relative risk of mortality. All the individual studies included in the all-cause mortality analysis enrolled less than 100 patients per treatment arm, and thus were not powered individually to detect a survival benefit of prophylaxis. In addition, trials of pre-specified high methodological quality (e.g., employing double-blinding) yielded smaller effect estimates of prophylaxis than ones of lower quality. In a
subsequent analysis of trials in neutropenic patients at higher risk (acute leukemia or bone marrow transplant recipients) and lower risk (solid tumors and lymphoma) of infectious complications, prophylaxis with quinolones was associated with survival benefit in both groups, but with a greater effect in the higher risk group (19).

The rate of Gram-positive infections and fungal infections was not significantly affected by quinolone prophylaxis in the meta-analysis by Engels et al. (16). This is an important consideration given the occurrence of an increased rate of Gram-positive infections in some prophylaxis trials using ciprofloxacin (3, 20), which has poor activity against streptococci. In patients with severe neutropenia (such as occurs following induction therapy for acute leukemia), prophylaxis with quinolones or TMP-SMX can increase the risk of viridans-group streptococcal bacteremia (21), which can cause severe sepsis in neutropenic patients.

Cullen et al. (13) conducted a trial of levofloxacin in patients who were receiving chemotherapy for solid tumors or lymphoma; 1,565 patients underwent randomization. The primary endpoint was the incidence of fever attributed to infection. Secondary outcomes included the incidence of all probable infections, severe infections, and hospitalization. During the first cycle of chemotherapy, 3.5% of levofloxacin recipients had at least one febrile episode versus 7.9% in the placebo group. During the entire chemotherapy course, 10.8% of levofloxacin recipients and 15.2% of placebo recipients developed fever. Hospitalization was required for the treatment of infection in 15.7% of levofloxacin and 21.6% of placebo recipients. Serious infections and infection-related mortality were rare in both groups.

A secondary analysis of this trial was performed to risk-stratify patients for development of neutropenic fever as a means to target prophylaxis to those who would derive the most benefit (22). Patients at highest risk for neutropenic fever were those receiving the first cycle of chemotherapy and those who developed neutropenic fever after the first cycle who went on to receive subsequent cycles. The rate of neutropenic fever was greatest for testicular cancer (27.9%), then small-cell lung cancer (17.3%), and lowest for breast cancer (11.5%). The authors advise prophylactic levofloxacin on cycle 1 only of chemotherapy and on subsequent cycles after a cycle-1 fever.

Bucaneve et al. (14) evaluated levofloxacin prophylaxis in patients in whom chemotherapy-induced neutropenia (<1,000 neutrophils/µl) was expected to last for more than 7 days. Levofloxacin prophylaxis was associated with a significant reduction in fever and microbiologically documented infections, bacteremias, and single-agent Gram-negative bacteremias compared with the placebo group while the survival rate was similar. The benefits of prophylaxis were similar between patients with acute leukemia and those with solid tumors or lymphoma.

Thus, the main advantage of levofloxacin prophylaxis in intermediate and higher risk patients with chemotherapy-induced neutropenia (defined as 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 neutropenic patients was a small, but statistically significant, reduction in fever and hospitalization for neutropenic fever (13).

### Disadvantages of quinolone prophylaxis

While there are clear benefits of quinolone prophylaxis in neutropenic patients, there are also important concerns (Table 1). The major concern of antibacterial prophylaxis is selection for resistant pathogens. This concern applies both to the

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Disadvantages</th>
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<tr>
<td>• ↓ incidence of neutropenic fever</td>
<td>• ↑ incidence of antibiotic-resistant pathogens has occurred at individual centers, but not observed in large trials or meta-analyses (see text)</td>
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<td>• ↓ incidence of Gram-negative rod infections in higher risk neutropenic patients</td>
<td>• Potential ↑ incidence of viridans-group streptococcal bacteremia in patients with acute leukemia receiving mucotoxic regimens (observed with ciprofloxacin prophylaxis)</td>
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<tr>
<td>• Potential ↓ incidence of hospitalizations for neutropenic fever</td>
<td>• Potential ↑ risk of C. difficile colitis</td>
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<tr>
<td>• Survival benefit shown in a meta-analysis, but not in individual randomized trials</td>
<td>• May preclude use of oral quinolone-based regimens as outpatient therapy for neutropenic fever</td>
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Abbreviation: C. difficile = Clostridium difficile.
individual patient receiving prophylaxis regarding the risk of breakthrough infections by antibiotic-resistant pathogens, and the potential for the spread of resistant pathogens within a hospital. A limitation of antimicrobial prophylactic trials is that they focus on short-term endpoints (e.g., incidence of neutropenic fever, infections, toxicity), but are not designed to evaluate the long-term effects on antimicrobial resistance. Although the frequency of quinolone-resistant Gram-negative isolates has not shown an increase in clinical trials or meta-analyses, individual studies have reported resistance problems occurring in the setting of broad quinolone prophylaxis. Quinolone-resistant Escherichia coli, P. aeruginosa (23, 24) and Stenotrophomonas maltophilia (25) have been associated with quinolone prophylaxis in some series. Gomez et al. (26) 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 due to a high prevalence of quinolone-resistant Enterobacteriaceae. There were no differences between the two 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. (27) reported that discontinuation of a policy of norfloxacin prophylaxis in an inpatient oncology ward was associated with a significant increase in the rate of quinolone-susceptible enterobacterial bloodstream infections, but there was no difference in the incidence of febrile neutropenia, fever of unknown origin or bacteremia during the first febrile episode.

Another concern of quinolone prophylaxis relates to the potential over-use of vancomycin. Although controversial, some centers may use vancomycin as initial empirical therapy for neutropenic fever in patients receiving quinolone prophylaxis with the rationale that quinolones provide effective protection against Gram-negative infections and increase the relative likelihood of a Gram-positive infection as the cause of fever (28). Increased vancomycin use raises substantial concern about selection for vancomycin-resistant enterococci and Staphylococcus aureus (29–31). The link between quinolone use and severe Clostridium difficile infections provides an additional cautionary note regarding excess use of quinolones (32–34).

Clinical studies have shown that quinolone prophylaxis can reduce the frequency of hospitalization for neutropenic fever, thereby reducing the cost of care. An important consideration for low risk patients with short durations of neutropenia is whether quinolone prophylaxis is of greater benefit than the option of an outpatient quinolone-based regimen (e.g., ciprofloxacin plus amoxicillin/clavulanate) for fever and neutropenia, should it occur. Recommended outpatient regimens for treatment of neutropenic fever in adults rely on the use of quinolones, and assume that fever will not develop while on quinolone prophylaxis. There are no evidence-based criteria to 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, therefore, potentially result in a higher frequency of hospitalization and intravenous antibiotics in patients who would otherwise be candidates for outpatient management.

Conclusions and recommendations
Taking these findings into consideration, what are the expected benefits and limitations of antibacterial prophylaxis for chemotherapy-induced neutropenia? The expected benefits will be a function of the underlying risk of infectious complications. In lower risk patients with neutropenia, the major benefit of quinolone prophylaxis relates to a reduction in the incidence of neutropenic fever. Reduction in episodes of neutropenic fever can translate into averting hospitalization for neutropenic fever. In addition, development of neutropenic fever can be a dose-limiting toxicity in experimental studies and, in routine clinical practice, can lead to reduction in the intensity of chemotherapy. In patients with prolonged neutropenia (e.g., lasting at least 7 days), the major benefit of prophylaxis is to reduce Gram-negative rod infections. Although not demonstrated in individual well-powered randomized trials, a meta-analysis showed that antibacterial prophylaxis during neutropenia can confer a survival benefit. The major potential disadvantages of antibiotic prophylaxis are the potential for selection for antibiotic-resistant pathogens, overuse of vancomycin as therapy for neutropenic fever, increased risk of C. difficile, and lack of evidence-based recommendations for outpatient oral antibiotic management of neutropenic fever.

These competing benefits and disadvantages of antibacterial prophylaxis have led to different recommendations in official guidelines. The 2002 Infectious Diseases Society of America (IDSA) guidelines on management of neutropenic fever advised against antibacterial prophylaxis in neutropenic patients (35). Although recognizing the benefits of prophylaxis, this recommendation was based on a concern about the emergence of antibiotic-resistant bacteria and the lack of a survival
benefit in randomized trials. The National Comprehensive Cancer Network (NCCN) guidelines recommend that quinolone prophylaxis be considered in adults with neutropenia at intermediate or high risk for infectious complications (36). This group would include neutropenic patients with hematological malignancies, stem cell transplant recipients, and an expected duration of neutropenia of at least 7 days. In neutropenic patients at high risk of *Pneumocystis jiroveci* infection (e.g., those receiving prolonged high-dose corticosteroids), prophylaxis with TMP-SMX is advised. Local patterns of antibiotic resistance and prior history of infections in individual patients should also be considered in decisions on antibiotic prophylaxis.

REFERENCES


