Preventing Invasive Bacterial Infection in Neutropenic Patients with Cancer

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Introduction
Children receiving myelosuppressive chemotherapy are at risk for febrile neutropenia, invasive infections and infection-related mortality. Risks for these different outcomes vary according to several factors including the depth and duration of neutropenia¹, presence of co-morbidities², and other clinical and laboratory markers.³⁻⁶ Children at high risk of infectious morbidity include those with acute myeloid leukemia (AML), relapsed acute lymphoblastic leukemia (ALL) and those receiving myeloablative hematopoietic stem cell transplantation (SCT). For example, pediatric AML treatment-related mortality ranges from 4 to 11%⁷, with most of this mortality attributed to infection. An infection-related mortality of 25/341 (7.3%) was reported for children treated according to MRC-10.⁸ The most recent Children’s Cancer Group (CCG) AML study, CCG 2961 reported 1,007 blood borne infection among 553 children receiving 1,243 courses of chemotherapy.⁹

Infectious outcomes including febrile neutropenia and invasive infections are clinically important outcomes that impact on costs, quality of life and mortality. Thus, interventions to prevent infectious outcomes have been tested in hundreds of randomized controlled trials (RCTs). This review will focus on two specific interventions to prevent invasive bacterial infections, namely prophylactic hematopoietic colony-stimulating factor (CSF) and prophylactic antimicrobial administration.

Colony stimulating factors
Granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) are hematopoietic CSFs that decrease the duration and severity of neutropenia in adults and children who receive chemotherapy for cancer.¹⁰,¹¹ However, elucidation of a target population who might particularly benefit from CSFs in terms of clinically important infectious outcomes continues to be refined. Initially, three large RCTs of adults receiving chemotherapy for cancer were particularly influential in early guideline development and recommendations for CSF utilization. These trials demonstrated reductions in the risk of febrile neutropenia from 77% to 40%,¹² 53% to 26%¹³ and 44% to 23%¹⁴ with CSF administration. In other words, these trials demonstrated that in adults receiving moderately intensive chemotherapy that resulted in a frequency of febrile neutropenia of 44% to 77% in the control arms, prophylactic G-CSF was associated with an approximately 50% reduction in febrile neutropenia.¹²⁻¹⁴ On the basis of these studies, early guidelines published by the American Society of Clinical Oncology (ASCO) suggested that CSFs be used as primary prophylaxis (before onset of neutropenia or febrile neutropenia) when the expected incidence of febrile neutropenia is 40% or more.¹¹,¹⁵,¹⁶

Subsequently, several systematic reviews have examined the question of whether CSFs are useful for cancer patients in the prophylactic setting. Lyman et al. conducted a meta-analysis of trials of prophylactic G-CSF in patients receiving dose-intensive chemotherapy for either solid tumors or malignant lymphomas.¹⁷ Eight randomized trials were identified. The use of G-CSF was associated with a reduction in febrile neutropenia, with an odds ratio (OR) of 0.38 (95% confidence interval [CI] 0.29 to 0.49; P = .001). G-CSF also was associated with a reduction in documented infections, with an OR of 0.51 (95% CI 0.36 to 0.73; P = .001). However, there was no reduction in infection-related mortality with an OR of 0.60 (95% CI 0.30 to 1.22; P = .2).¹⁷

In addition to the systematic review conducted by Lyman, there also have been meta-analyses
performed within specific diagnostic sub-groups. For example, Bohlius et al. performed a meta-analysis of prophylactic G-CSF and GM-CSF in patients with malignant lymphoma.\textsuperscript{18} Eleven randomized trials were included. In this review, CSFs reduced the risk of febrile neutropenia, with a relative risk (RR) of 0.64 (95\% CI 0.55 to 0.75). In addition, CSFs reduced the risk of febrile neutropenia (RR 0.74, 95\% CI 0.62 to 0.89) and microbiologically documented infection (RR 0.74, 95\% CI 0.64 to 0.85). However, CSFs did not affect either overall mortality during chemotherapy (RR 1.21, 95\% CI 0.70 to 2.10) or infection-related mortality (RR 2.07, 95\% CI 0.81 to 5.34). Furthermore, CSFs were not associated with a benefit in terms of overall survival at an average observation time of four years (hazard ratio [HR] 0.97, 95\% CI 0.81 to 1.17).\textsuperscript{18} These authors later updated their meta-analysis to include 12 randomized trials; the results of this meta-analysis were qualitatively similar to those of their previous publication.\textsuperscript{19}

In another population, Berghmans and colleagues examined 12 RCTs of prophylactic CSFs in small cell lung cancer.\textsuperscript{20} CSFs were not associated with improved survival.\textsuperscript{20} Adams et al. reviewed cost-effectiveness models of prophylactic G-CSF use in this population. The frequency of febrile neutropenia in the control arm required to result in cost saving associated with G-CSF use ranged from 35 to 70\%.\textsuperscript{21}

In another systematic review, the results of 16 RCTs of prophylactic CSFs in pediatric cancer patients were synthesized.\textsuperscript{22} The mean rate of febrile neutropenia in the control arms was 57\% (range 39 to 100\%). Using a random effects model, CSFs were associated with a 20\% reduction in febrile neutropenia, with a rate ratio of 0.80 (95\% CI 0.67 to 0.95; P = .01), and a decrease in hospitalization length, with a weighted mean difference (WMD) of –1.9 (95\% CI –2.7 to -1.1 days; P < 0.00001). CSF use also was associated with reduction in documented infections (rate ratio 0.78, 95\% CI 0.62 to 0.97; P = .02) and reduction in amphotericin B use (rate ratio 0.50, 95\% CI 0.28 to 0.87; P = .02). There was no difference in duration of parenteral antibiotic therapy (WMD –4.29, 95\% CI -10.60 to 2.02 days; P = 0.2) or infection-related mortality (rate ratio 1.02, 95\% CI 0.34 to 3.06; P = 0.97).\textsuperscript{22}

Using a stratified analysis, this systematic review suggested that the effects of G-CSF and GM-CSF were similar. However, a secondary analysis using the same data found that G-CSFs may be associated with more clinical benefits. Specifically, this second meta-analysis found that there was a 90\% probability that G-CSF was more effective than GM-CSF in reducing the rate of febrile neutropenia. G-CSF also was associated with a 4.8 day greater decrease in duration of parenteral antibiotic therapy compared to GM-CSF and there was a 98\% probability that G-CSF was better than GM-CSF with respect to this outcome.\textsuperscript{22,23}

A second pediatric meta-analysis of prophylactic CSFs was conducted in children with ALL.\textsuperscript{24} Six studies of 332 children were included. The use of CSFs reduced the risk of febrile neutropenia (rate ratio 0.63, 95\% CI 0.46 to 0.85; P = .003), duration of hospitalization (WMD -1.58, 95\% CI -3.00 to -0.15; P = .03) and number of infections (rate ratio 0.44, 95\% CI 0.24 to 0.80; P = .002).\textsuperscript{24}

Up until this point, given that clinically important benefits with the prophylactic administration of CSFs had been demonstrated only following administration of more intensive chemotherapy, and since recipients of SCT almost universally experience febrile neutropenia, we postulated that this group of patients might particularly benefit from prophylactic CSF administration. Thus, we conducted a meta-analysis of prophylactic CSF administration in the SCT setting. There were 34 included studies based on pre-defined inclusion criteria. CSFs reduced the risk of documented infections (RR 0.87, 95\% CI 0.76 to 1.00; P = .05) and duration of parenteral antibiotics (WMD -1.39 days, 95\% CI -2.56 to -0.22; P = .02) but did not reduce infection-related mortality (RR 0.76, 95\% CI 0.41 to 1.44; P = .4).

In summary, the results of many RCTs and meta-analyses have found a consistent benefit of prophylactic CSF administration in preventing febrile neutropenia and invasive bacterial infections. So far, a reduction in infection-related mortality has not been demonstrated. The target population who would benefit most from prophylactic CSFs remains to be defined. Although intuitively recipients of SCT may have been expected to benefit most from CSF administration, the data have not supported this hypothesis. It is possible that those with extreme
degrees of myelosuppression benefit less than those with more intermediate risks of febrile neutropenia (i.e. between 40% and 80%). However, such a hypothesis remains to be confirmed.

**Antibiotic prophylaxis**

A second intervention of interest has been prophylactic administration of antibiotics to prevent invasive bacterial infections. Current guidelines do not recommend routine antibiotic prophylaxis in cancer patients. However, a survey conducted by the Japan Adult Leukemia Study Group in 2001 that included 196 hospitals found that 38% of physicians used an oral quinolone for antibacterial prophylaxis in patients with leukemia. While the bulk of RCTs examining this question extend back over the last three decades, recent RCTs and meta-analyses have continued to add to the controversy.

Most interest has been directed at fluoroquinolones because of their broad antimicrobial spectrum, preservation of the anaerobic flora of the alimentary tract, high concentration in the feces, systemic bactericidal activity, good tolerability and lack of myelosuppression.

The first two meta-analyses to address this topic both demonstrated a reduction in Gram negative bacteremia but no affect on infection-related mortality. More specifically, Engels and colleagues included 18 studies of quinolone prophylaxis and showed a reduction in Gram negative infections (RR 0.21, 95% CI 0.12 to 0.37), microbiologically documented infections (RR 0.65, 95% CI 0.50 to 0.85), total infections (RR 0.54, 95% CI 0.31 to 0.95) and fevers (RR 0.85, 95% CI 0.73 to 0.99). Cruciani et al. included 19 studies and similarly showed fluoroquinolones prevented Gram negative bacteremia (OR 0.09, 95% CI 0.05 to 0.16). Neither study demonstrated a reduction in infection-related mortality.

Two subsequent meta-analyses of prophylactic antibiotic administration did show reductions in infection-related mortality. First, van de Wetering et al. examined 21 trials of oral prophylaxis antibiotics in neutropenic febrile oncology patients. Prophylaxis reduced bacteremia (OR 0.48, 95% CI 0.34 to 0.66) and Gram negative bacteremia (OR 0.39, 95% CI 0.24 to 0.62). Most importantly, this analysis demonstrated a reduction in infection-related mortality, with an OR of 0.56 (95% CI 0.34 to 0.96). The most recent trial included in this systematic review was published in 2002.

Finally, Gafter-Gvili et al. conducted the largest meta-analysis of prophylactic antimicrobial administration in cancer patients and specifically examined the efficacy of administration on survival. They included randomized trials comparing antibiotic therapy with placebo, no intervention or another antibiotic for prophylaxis of bacterial infections in neutropenic patients. The primary outcome was all-cause mortality by the end of follow-up defined in each study. Secondary outcomes included infection-related death, febrile episodes, clinically documented infection, microbiologically documented infection, bacteremia, adverse effects and emergence of resistant bacteria. In total, 95 studies performed between 1973 and 2004 were included and 9,283 patients were randomized. Fifty trials compared a prophylactic antibiotic with placebo or no intervention, of which 17 trials evaluated fluoroquinolones. Prophylaxis was initiated either when the patient became neutropenic (17 trials) or with the initiation of chemotherapy (78 trials). In all but two trials, prophylaxis was continued until resolution of neutropenia, fever or remission developed, or the patient received a maximum of 6 weeks of treatment. Overall, antibiotic prophylaxis decreased the risk of death with a RR of 0.67 (95% CI 0.55 to 0.81). In addition, prophylaxis was associated with reductions in infection-related death (RR 0.58, 95% CI .55 to .81), fever (RR 0.79, 95% CI 0.75 to 0.82), clinically documented infections (RR 0.64, 95% CI 0.60 to 0.71), microbiologically documented infections (RR 0.54, 95% CI 0.49 to 0.60), Gram negative infections (RR 0.39, 95% CI 0.32 to 0.46), Gram positive infections (RR 0.42, 95% CI 0.35 to 0.50), and bacteremia (RR 0.052, 95% CI 0.46 to 0.59). Prophylaxis was not associated with increased fungal infection (RR 1.07, 95% CI 0.83 to 1.37). However, prophylaxis was associated with more adverse events (RR 1.57, 95% CI 1.33 to 1.86). The most recent included trial was published in 2003.
An important question relating to these meta-analyses is whether the results are applicable today given that most of the included studies were conducted over a decade ago. Over the last three decades, initially Gram negative pathogens predominated as a cause of morbidity and mortality in febrile neutropenic patients. Over time, the incidence of Gram positive infections has increased along with a world-wide increase in the incidence of viridans group streptococcal infection. Two recently conducted RCTs have tried to address this issue. In both studies, levofloxacin was the prophylactic agent studied.

Bucaneve and colleagues examined a high risk population who were expected to be neutropenic for greater than 7 days. They assigned 760 consecutive adult patients with cancer to receive oral levofloxacin or placebo from start of chemotherapy until resolution of neutropenia. Antibiotic prophylaxis was associated with a reduction in fever from 85% with placebo to 65% with levofloxacin (RR 0.76, P=.001). In addition, lower rates of microbiologically documented infection, bacteremia and single-agent Gram negative bacteremia were demonstrated. However, mortality was similar, occurring in 10/373 (3%) with levofloxacin versus 18/363 (5%) with placebo (P=.15). Infection-related mortality also was similar, occurring in 9/373 (2%) with levofloxacin versus 14/363 (4%) with placebo.

In contrast, the second recent RCT by Cullen and colleagues examined a low risk population and included those receiving chemotherapy for solid tumors and lymphomas. This study allocated 1,565 subjects to levofloxacin or placebo for 7 days during expected neutropenia. They demonstrated a 4.4% decrease in the prevalence of febrile episodes attributable to infection in the first cycle and a 4.4% decrease in the cumulative incidence of any febrile episode. However, the baseline risk of clinically documented febrile episodes attributable to infection in the first cycle was only 7.9%. Four patients died in each group.

Given these results, it is likely that there is a patient population who is expected to derive meaningful benefit from prophylactic antibiotic administration. However, any potential benefit must be weighed against adverse events, particularly in terms of increasing antimicrobial resistance. Since infections with resistant microorganisms tend to be associated with worse outcomes, non-discriminate use of antibiotic prophylaxis may cause worse infectious outcomes for later cohorts of patients. Thus, future work will likely focus on identification of a patient population who is most likely to benefit from antibiotic prophylaxis. Furthermore, the optimal period for prophylaxis has yet to be defined. For example, it is likely that prophylaxis could be discontinued upon evidence of bone marrow recovery which would be associated with less antimicrobial administration compared to waiting until resolution of neutropenia.

**Summary**

The last three decades has seen a plethora of RCTs with the primary aim of reducing infections in neutropenic cancer patients. While CSFs can reduce invasive infections, prophylaxis has not been demonstrated to improve survival. In contrast, prophylactic antibiotics can reduce mortality. However, concerns about whether the results are generalizable to the current microbiological milieu and the potential for antimicrobial resistance have limited its widespread adoption. Future research will likely focus on identifying patient populations more likely to benefit from a particular intervention while balancing costs and issues of drug resistance.

**References**


