Preventing Fever and Mortality with Fluoroquinolone Prophylaxis in Neutropenic Cancer Patients being Treated with Chemotherapy

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Abstract
Background: Neutropenia is the most common adverse effect of chemotherapy treatment but is often necessary to destroy malignant disorders and neoplasms. As a patient undergoes most chemotherapeutic regimens, myelosuppression occurs and reduces the patient’s ability to fight infection from harmful pathogens. As neutropenia worsens, enteric flora are able to invade and proliferate, and opportunistic bacteria can cause new infections. Antibiotics are available as focused and empiric treatment for these infections but are not recommended for use in prevention. The use of antibiotics as prophylaxis in cancer patients with neutropenia is controversial with published data supporting many conclusions.

Hypothesis: Current data available over the last decade is bringing consensus to prevention of fever and mortality with the prophylactic use of fluoroquinolones in neutropenic cancer patients. It is hypothesized that a review of this newer set of data will confirm the efficacy of fluoroquinolones as prevention of fever and mortality in this patient population.

Study Design: A systematic review was performed to examine the pertinent published literature.

Methods: Inclusion keywords were determined for searching articles among multiple databases. Studies eligible for inclusion into this review must be using a fluoroquinolone for prophylaxis in neutropenic cancer patients receiving chemotherapy, be randomized controlled trials in the English language, and have a publication date no earlier than the year 2000. Standard evidence based medicine critical review appraisals were applied as well as scoring according to Jadad analysis to assess quality and validity of each study. Relative risk, relative risk reduction, absolute risk reduction, number needed to treat, and a precision index were calculated or included, as available. Qualitative weighting of these assessments was made during discussion and conclusion.

Results: The review of literature and use of inclusion and exclusion criteria yielded six pertinent articles with patient populations ranging from 70 to 1,565 individuals (Table I). The relative risk for fever or infection ranged from 0.19 (p < 0.001) to 0.81 (p = 0.02) and for mortality ranged from 0.0 (p = 0.022) to 0.60 (95% CI -0.05 to 0.005). Number needed to treat ranged from 3.1 to 22.7 for fever, and from 4.5 to 100 for mortality. Jadad scoring ranged between 1 and 5 (out of 5) with two trials scoring ≤2 and 4 trials scoring ≥4.

Conclusion: After weighing the results of EBM reviews, Jadad scoring, and conclusive findings of these studies, there is more evidence that prophylactic use of fluoroquinolones prevents fever and mortality in treatment groups compared to control groups, with benefit increasing as severity of myelosuppression increases. According to this systematic review, prophylactic fluoroquinolone use for prevention of fever is recommended for all neutropenic cancer patients receiving chemotherapy.

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Preventing Fever and Mortality with Fluoroquinolone Prophylaxis in Neutropenic Cancer Patients being Treated with Chemotherapy

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A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

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Clinical Graduate Project Coordinators:
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Abstract

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Conclusion: After weighing the results of EBM reviews, Jadad scoring, and conclusive findings of these studies, there is more evidence that prophylactic use of fluoroquinolones prevents fever and mortality in treatment groups compared to control groups, with benefit increasing as severity of myelosuppression increases. According to this systematic review, prophylactic fluoroquinolone use for prevention of fever is recommended for all neutropenic cancer patients receiving chemotherapy.

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Preventing Fever and Mortality with Fluoroquinolone Prophylaxis in Neutropenic Cancer Patients being Treated with Chemotherapy

Introduction

The treatment of hematological malignancies and solid tumor neoplasms with chemotherapeutic agents has been a significant part of the fight against cancer since World War I with the discovery of myelosuppression from mustard gas toxicity. It was noted that mustard gas would suppress lymphoid and myeloid cell lines and that this may have been a vital aid in prolonging survival in lymphoma patients. In the early 1940s, human clinical trials in the United States and Great Britain had begun to investigate treatment of lymphomas, leukemias, and solid tumors through lymphoid and myeloid suppression by nitrogen mustard.

Since then, the science of chemotherapy as a treatment for cancers has exploded with complex pharmacologic developments that allow for destruction of cancer cells but often with narrow therapeutic indices. It is a challenge to destroy the malignancy while keeping the patient’s own cells alive and functioning. Neutropenia is most often the result of chemotherapy and has become an unavoidable complication of cancer treatment today.

Myelosuppression resulting in neutropenia, anemia, and thrombocytopenia is common with many regimens of chemotherapy. The nadir for white blood cells (WBC) occurs between 5 and 14 days following initiation of chemotherapy and mostly recovers by 7 to 21 days. This will vary depending on the pharmacologic agent prescribed and the dosing regimen. Neutropenia, though expected, complicates treatment by lowering the patient’s ability to fight off microbial infection and is typically the dose limiting complication of chemotherapy administration. Fever and severe infection are common,
and these immunocompromised patients are often admitted to the hospital and given empiric wide spectrum intravenous antibiotics, at significant cost, to fight these complications. Morbidity and mortality may occur from bacterial sepsis and from localized infections such as pneumonia, until neutrophil counts improve and the patient is no longer immunocompromised.

Neutropenia is generally defined as an absolute neutrophil count (ANC) less than 1500 cells/µL, with a significant decrease in ability to fight infection at less than 1000 cells/µL, which is considered severe neutropenia. At less than 500 cells/µL, life threatening infection is imminent from endogenous flora; particularly from enteric gram negative bacteria (GNB). Diagnosis of infection may be made by simple clinical objective findings, or through specific known focal site of infection that may or may not include microbial isolation through blood, sputum, or local cultures.

Febrile neutropenia (FN) varies in definition but typically is considered to be diagnostic in patients with neutropenia and temperature greater than 38°C for one hour or one episode at 38.3°C. Infections in the neutropenic patient are most often bacterial in origin, but may also include viral and fungal etiology. Common bacterial pathogens in FN are often from systemic seeding of endogenous enteric flora but also include P. aeruginosa or gram positive species.

Prophylaxis with antibiotics for patients with expected neutropenia after chemotherapy is an area of medicine that comes with some disagreement. The National Comprehensive Cancer Network (NCCN), the national authority for protocol in cancer care, has set guidelines that stratify three risk levels: low, intermediate, and high. These risk levels are determined by the type of cancer and the treatment to be administered, and
have different levels of recommended prophylaxis. According to the NCCN, low risk patients do not need bacterial prophylaxis, and intermediate and high risk patients may benefit from fluoroquinolone prophylaxis.5

Fluoroquinolones are chosen for their wide spectrum coverage that includes GNB, simple dosing, and generally well tolerated adverse effects. The fluoroquinolones, as a class, are bactericidal with a mechanism of action that inhibits replication of bacterial DNA through interference with DNA gyrase and topoisomerase IV. Typical fluoroquinolones used in practice include ciprofloxacin, norfloxacin, levofloxacin, and moxifloxacin. Organisms resistant to fluoroquinolones do exist, and include methicillin resistant *Staph aureus*, *Pseudomonas*, coagulase-negative *Staphylococci*, and *Enterococci*.6 Increase in resistance in this impressive antibacterial class is of concern when considering possibly unnecessary prophylaxis.

Recent polling of practicing oncologists suggests that NCCN guidelines are not adhered to, and that clinical judgment and experience is often substituted when considering prophylaxis in low risk category patients. Of 1,207 oncologist respondents to a national survey in regards to antibiotic treatment and FN, a subset showed that fluoroquinolone prophylactic antibiotics are used in 45% of afebrile low risk patients.7 While there are guidelines that are currently established and available, it would seem there is still either confusion, or disagreement on the evidence behind these rules.

Much has been published on the use of prophylactic antibiotics in neutropenic cancer patients, in articles ranging from strict randomized controlled trials, to case studies, and reviews, over the past several decades. Consensus is narrowing, especially with the publication of two large placebo controlled randomized trials in 2005 which
agreed that levofloxacin prophylaxis in afebrile neutropenic cancer patients was of significant benefit.\textsuperscript{8,9} In order to bring together the pertinent evidence available today and to answer a clinical question in regards to prevention of infection in neutropenic cancer patients, a systematic review was performed of randomized controlled trials that investigated the use of fluoroquinolones in this patient population. Does fluoroquinolone prophylaxis prevent fever and mortality in neutropenic cancer patients being treated with chemotherapy?

**Methods**

**Inclusion and Exclusion Criteria:**

Trials included in this review were published randomized controlled trials that focused on the use of fluoroquinolones in the case of neutropenic cancer patients. The included trials were not limited by age or demographic, with the only requirement of the selected population being human neutropenia in the setting of a cancer diagnosis. Selected trials met these criteria were in the English language with a publication date no earlier than the year 2000. Excluded from this study were meta-analysis or systematic review articles, comment or anecdotal articles, and studies using fluoroquinolones as a second line intervention.

**Literature Search:**

A search of the available literature was performed using MEDLINE-OvidSP, CINAHL, Web of Science, BIOSIS, and PubMed databases. Search terms included neutropenia, fluoroquinolones, and antibiotic prophylaxis, and were limited to English
language, randomized controlled trials, human subjects, with a date range of year 2000 to the present. The reference sections of eligible trials were also scrutinized for additional sources.

**Evidence Based Medicine (EBM) reviews:**

Eligible studies were reviewed using JAMAevidence EBM review forms for therapy, and following Centre for Health Evidence at the University of Alberta Users’ Guides to Evidence-Based Practice.\(^\text{10}\) Relative risk (RR), relative risk reduction (RRR), absolute risk reduction (ARR), and number needed to treat (NNT) were calculated based on available data from the included studies. Additional evaluation using the Jadad scoring method was implemented, with a numerical score of 0-5 measuring the quality of each article.\(^\text{11}\) Based on these reviews and scoring methods, conclusions were made in regards to the clinical question of effectiveness of fluoroquinolones in preventing fever and mortality in neutropenic cancer patients being treated with chemotherapy.

**Results**

Search results after inclusion and exclusion criteria were examined, yielded 6 articles to be reviewed (See Table I).\(^\text{8,9,12-15}\) In these studies, patient populations ranging from 70 to 1,565 individuals between 16 and 18 years of age, were randomized into treatment and control groups. All were undergoing chemotherapy for a range of illnesses that included small-cell lung cancer (SCLC), solid tumors, acute leukemia, lymphoma, and other hematological malignancies. Those receiving conditioning preparation for bone marrow transplant (BMT) were also included in several of the studies. The
definition of neutropenia was consistently defined as ANC < 1000 cells/µL with the exception of the largest study and its follow-up analysis, which defined neutropenia as ANC < 500 cells/µL.\textsuperscript{8,12} Fever definition ranged from >38°C for one episode, with temperatures taken at different sites\textsuperscript{8,12} to >38.5°C for one episode.\textsuperscript{9} One study did not provide their definition of fever.\textsuperscript{15}

Intervention with prophylactic fluoroquinolone antibiotics was used in each study with three articles using ciprofloxacin (dosing 500 twice daily to 750 twice daily)\textsuperscript{13-15} and two articles plus follow-up analysis using levofloxacin at 500mg daily.\textsuperscript{8,9,12} Two studies used additional antibiotic prophylaxis for improved gram positive coverage, including roxithromycin and colistin.\textsuperscript{13,14} Matching placebo comparison was used in all but one study, which compared fluoroquinolone prophylaxis to an aminoglycoside (neomycin).\textsuperscript{13} Start times for the prophylactic regimen ranged from 1 to 3 days prior to chemotherapy initiation, to as late as day 14 days after initiation. In one study it was unspecified at which time prophylactic therapy was initiated.\textsuperscript{13}

The end point of intervention was determined by multiple methods, including: discontinuation at day 13 of cycle,\textsuperscript{14} for ANC ≥ 1.0 x 10\textsuperscript{9}/L or after a maximum of 30 days,\textsuperscript{13} for ANC > 1.0 x 10\textsuperscript{9}/L,\textsuperscript{9,15} or after 7 consecutive days of treatment.\textsuperscript{8,12} Each study also had endpoints that included fever requiring empiric intravenous antibiotic use, with the exception of the SIGNIFICANT (Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/− Antibiotic in a Number of Tumours) trial group, whose paper was published by Cullen et al, which required 7 days of consecutive treatment.\textsuperscript{8,12} In one study, data from the SIGNIFICANT trial group was
further analyzed to determine the effect of a fluoroquinolone on febrile episodes according to subgroups including cancer type, age, sex, and other factors.\textsuperscript{12}

The EBM critical appraisal reviews and Jadad scoring of these articles reflect a range of quality that makes consensus on prevention in these patients difficult. However, the larger trials are very well designed and documented, and are accordingly given more qualitative weight when making conclusions. Quality assessment is performed using EBM criteria that monitors markers such as randomization, control of populations and accountability at outcome, methods of blinding, and similarity of treatment of groups (see Table II). These items are essential in designing and reporting randomized controlled trials for publication and use by medical professionals. Furthermore, calculations for EBM review and scoring according to Jadad method can be found in Table III for a numerical evaluation of the published results.

The article written by Tjan-Heijnen et al was designed to determine reduction in FN through the prophylactic use of ciprofloxacin plus roxithromycin in comparison to matching placebo in SCLC patients. It was concluded in the trial that a prophylactic regimen with ciprofloxacin and roxithromycin are effective at reducing episodes of FN in SCLC patients in comparison to placebo, and can be recommended for use. The trial was randomized through minimization and followed a population of 161 adults through to completion. All patients were accounted for at the end of the trial and there was no apparent cross-over during analysis. Double-blinding was achieved by sealing the placebo versus treatment roster, and by providing a treatment pack distributed by a data center. The treatment and control groups were similar, although limited information was given and no \( p \) values were assigned to determine if differences were significant or not.
Both groups were treated equally throughout the trial, with contingent plans for adverse effects or persistent fever. Relative risk was 0.56 for fever with a $p$ value of 0.007 and there were no deaths in the treatment group while 6 patients died in the control group ($p = 0.022$). Number needed to treat was calculated to be 5.3 for fever and 16.7 for death. Jadad scoring was determined to be 5 out of 5 on the basis of description of appropriate randomization, description of appropriate double-blinding, and all patients being accounted for through completion of their study.$^{14}$

Prentice et al completed a study that would show prophylaxis against bacterial infection using ciprofloxacin plus colistin as the treatment intervention, and neomycin plus colistin as the comparison control group. This article examined 150 adults with hematological malignancy and concluded that their treatment was effective in prevention of GNB infection. A secondary finding was, that no significant resistant bacterial strains were isolated at a two year follow up. This trial was unfortunately the weakest of those reviewed here as it did not adequately address important issues such as method of randomization, accountability of population at conclusion, nor the method of blinding. It was also noted that 73% of patients in the treatment group developed fever and 90% in the control group developed fever. These were the highest percentages of patients with fever of any of the studies presented here. Treatment and control groups were however, treated equally and relative risk was determined to be 0.81 ($p = 0.02$) for fever and 0.37 for death ($p$ unknown, no CI provided). Number needed to treat was calculated to be 5.9 to prevent fever and 58.8 to prevent death. Jadad scoring was determined to be 1 out of 5 as the method of randomization was unknown, the population at conclusion was not well documented, and it is not certain whether patients were truly blinded for this study.$^{13}$
In the study by Nenova et al, the drugs used were of the fluoroquinolone class but different patients received different fluoroquinolones, with ciprofloxacin being the predominant regimen (48.8% of patients). This study attempted to evaluate prophylaxis using fluoroquinolones initiated at the onset of neutropenia and the conclusion was reached that this does reduce risk for infection without significant difference in survival versus placebo. This study also evaluated mortality at one month following chemotherapy initiation and found that the reduction of mortality was significant in the treatment group. This trial consisted of 70 adults in an open prospective randomized trial. The method of randomization is not specified and single-blinding of patients was achieved through undescribed placebo. Follow up is complete with all patients receiving follow up for months 1 to 100 after chemotherapy. In regards to similarity of groups, there may be differences in gender and type of malignancy between the treatment and control groups, but $p$ values are not given to evaluate if this is statistically significant. Treatment of both test and control groups is equal. Relative risk for infection (fever) and mortality in the first month were calculated as 0.19 and 0.21 respectively ($p<0.001$ and $p<0.01$). Number needed to treat for infection and fever is 3.1 and for death in the first month NNT is 4.5. Jadad scoring is 2 out of 5 as the article does not adequately describe randomization and the trial is not double-blinded.\textsuperscript{15}

The largest study of those reviewed, conducted by Cullen et al, includes 1,565 patients with solid tumors and lymphomas. The treatment group was given levofloxacin daily for seven consecutive days as an equal regimen for all patients in the group. Conclusion was made that levofloxacin reduces neutropenic fever, infection, and hospitalization. The patients were adequately randomized using a computerized
minimization algorithm, and double-blinding was accomplished and described as matching placebo and by sealing of randomization codes. All patients were accounted for at the end of follow-up and were described using a table. The groups were similar and treated equally throughout the trial although no p values are given in Table 1 of the article. For fever during the first chemotherapy cycle, the relative risk is 0.44 (95% CI 0.28 to 0.68) and for overall severe infection or death, the relative risk is 0.50 (95% CI 0.22 to 1.17). In this study, number needed to treat to prevent fever during the first cycle was calculated to be 22.7, and for severe infection or death was found to be 100. Jadad scoring of 5 out of 5 was given for superior documentation of methods including randomization, blinding, and accountability of all participants.8

In the GIMEMA (Gruppo Italiano Malattie Ematologiche dell’Adulto) trial by Bucaneve et al, 760 adults were randomized to either levofloxacin daily or an identical placebo, to determine the prophylactic benefit in patients with acute leukemia, solid tumors, or lymphomas. Prophylactic treatment was started 1 to 3 days prior to chemotherapy and continued until patients were no longer neutropenic. Participants were randomized using a computer generated random number program and the study was described as double-blinded with description of placebo and comment on blinding of evaluators. The patient population was complete and accounted for at the end of follow up as seen in the provided table, and both the treatment and control groups appear to be equal, although again there were no p values provided to describe statistical significance of differences. All participants were treated equally throughout the trial. In regards to findings, relative risk was calculated to be 0.76 for fever (95% CI -0.26 to -0.14) and 0.60 for death (95% CI -0.05 to 0.005). The number needed to treat for successful prophylaxis
of fever was calculated to be 5 and for death was 50. Jadad scoring of this study was 5 out of 5 due to the excellent method of describing randomization, blinding, and documentation of patients at the conclusion of the study.9

This last trial was based on the data published in the SIGNIFICANT trial by Cullen et al, but was different, in that outcomes for specific subgroups were analyzed to determine whether or not the results would vary, when comparing the subgroups to the group as a whole. The subgroups included cancer type, age, gender, cycle number, and other factors to be evaluated. Cancer types included breast, testicular, SCLC, non-Hodgkin’s lymphoma (NHL), and a category to represent other types. The fresh examination of data concluded that, certain subgroups benefit more than others from bacterial prophylaxis using levofloxacin. Patients in their first cycle of chemotherapy, or who have breast, testicular, and SCLC achieve the greatest benefit. Original design and data collection of this study is the same as for the SIGNIFICANT trial. Data to perform review calculations on the subgroups was not available, however, odds ratios with 95% confidence intervals were provided in the study. For breast cancer the odds ratio was 0.26 (95% CI 0.09 to 0.79). The odds ratio for testicular cancer was found to be 0.39 (95% CI 0.17 to 0.90) and for SCLC the odds ratio is 0.09 (95% CI 0.01 to 0.73). The only subgroup that was found to possibly have disadvantage from prophylactic levofloxacin was the NHL subgroup with odds ratio 0.55 (95% CI 0.38 to 5.17). Jadad scoring for this study is the same as for the SIGNIFICANT trial at 5 out of 5.8,12
Discussion

This systematic review was performed to answer a clinical question about prevention of fever and mortality in neutropenic cancer patients receiving chemotherapy, through the use of prophylactic fluoroquinolones. Current guidelines by the NCCN, last updated in 2008, state that low risk patients do not need bacterial prophylaxis, while intermediate and high risk patients may benefit from fluoroquinolone prophylaxis. Although guidelines for bacterial prophylaxis in this group of patients are established, there is clearly a continuing need for clinical consistency in practice. Recent evidence within the last decade has contradicted many prior studies from the 80s and 90s and also supported many studies from the same period. Current guidelines state that not all cancer patients with expected neutropenia secondary to chemotherapy should be considered for antibiotic prophylaxis, but recent literature presents a challenge to these rules. In each of the studies reviewed in this paper it has been concluded that prevention of fever with fluoroquinolone use in neutropenic cancer patients treated with chemotherapy is significantly effective as opposed to their respective control groups. Two of the studies reviewed contain significant evidence that for their patient population and intervention, rates of mortality are also decreased in comparison to placebo. However, before a jump to prophylaxis for all neutropenic cancer patients is made, discussion must be conducted as to the validity and quality of each of these recently published trials.

The study by Prentice et al was not performed and documented appropriately according to established EBM review criteria (Table II) and to the Jadad score of 1 out of 5. At times it was difficult to determine how the patient populations were analyzed, and while conclusions were made, many of the standard methods of creating a double-blinded
placebo controlled randomized clinical trial were neither adhered to, nor documented. The use of ciprofloxacin plus colistin in comparison to neomycin plus colistin did evidence reduction of febrile episodes in the patient population. Analysis of mortality between the two populations was not performed. Given the overall quality of the study, it is difficult to rely on its conclusions when answering the clinical question, or to follow its recommendations when applying results to the patient population. The quality and validity do not provide confidence in the end conclusion and if using this study by itself, it would not be recommended to use fluoroquinolone prophylaxis in neutropenic cancer patients.

In contrast, the trial by Tjan-Heijnen et al was not perfect either but was designed and documented well. EBM review of the article and Jadad scoring (4 out of 5) gives confidence in the published results. There was no confusion in the article as to patient populations, methods, follow up, or conclusions, and the authors provided effective evidence that prophylactic ciprofloxacin plus roxithromycin is useful in the prevention of fever and mortality in adult SCLC patients receiving chemotherapy. This is one of two studies reviewed which supports the prophylactic use of fluoroquinolones in the reduction of mortality in neutropenic cancer patients. They have shown that incidence of death is decreased in their patient population due to the intervention. This is also the only study which has a patient population with a single specific form of cancer, a solid tumor type that demands extensive myelosuppressive chemotherapy. The regimen used in this study was cyclophosphamide, doxorubicin, and etoposide (CDE), and the participants were grouped into intensive versus standard therapy, based on their disease status. The advantage of using the intervention in the patients was seen most markedly in the
intensive therapy group, whose myelosuppression would have presumably been more substantial. In current practice, oncologists have moved from toxic three drug regimens such as CDE, to two drug therapy such as carboplatin and etoposide, with resulting improved levels of myelosuppression. The data in this article, while well designed and valid, may not be representative outside a population of SCLC patients with severe disease receiving highly myelosuppressive chemotherapy. In applying the conclusions to a wide population of patients undergoing chemotherapy, reservations should be apparent. It should be noted however, that conclusions can be drawn from this research that patients with impressive and significant levels of myelosuppression secondary to chemotherapy treatment, may benefit the greatest from fluoroquinolone prophylaxis. From the data presented in this article, it would be recommended that fluoroquinolone prophylaxis be used with a second agent that increases gram positive coverage to prevent fever and mortality in neutropenic cancer patients receiving chemotherapy, if severe levels of myelosuppression are predicted.

Nenova et al used multiple different fluoroquinolones as intervention in their trial versus placebo and produced a study that was moderately well designed and documented. Reviewing criteria for EBM quality and including Jadad scoring (2 out of 5) suggests weakness of this trial involving adults with hematological malignancies. Produced at the Medical University, Plovdiv, Bulgaria, this study was the most difficult to come by but certainly meets inclusion and exclusion criteria and warrants integration into the review. The authors came to the conclusion that both fever and mortality are reduced through prophylactic use of fluoroquinolones in neutropenic cancer patients. There are issues however, with this publication, most notably in the use of multiple different
fluoroquinolones without substantial documentation. Definition of fever was also unspecified throughout the article, and when looking at endpoints of febrile episodes and assumed infections, this definition should have been included. The trial was also an open trial, but it was indicated that patients were at least blinded through placebo. Open trials lower confidence in outcomes due to likely bias in providers and evaluators. Nevertheless, open trials are still useful and should be considered in context with other available research. There is also a question of whether or not possible differences in demographics of the two trial groups existed. Both gender and type of malignancy may be statistically different, but \( p \) values were not calculated or given. Despite some drawbacks to this trial, it does carry weight and it is recommended as partial evidence for fluoroquinolone prophylaxis of fever and mortality in neutropenic cancer patients receiving chemotherapy.

The remaining trials to be discussed are the most current evidence and the largest of all the trials included in this review. They are also by far the best designed, implemented, and documented and therefore, carry the most weight in drawing final conclusions. Both the SIGNIFICANT trial\(^8,12\) and the GIMEMA trial\(^9\) were published in the same issue of The New England Journal Of Medicine, as a direct challenge to existing thought on prophylaxis in neutropenic cancer patients. They have successfully done just that by both arriving at the conclusion that prophylaxis with levofloxacin (a fluoroquinolone) in neutropenic cancer patients is effective and recommended. Both studies also came to the conclusion that there is no significant difference in mortality between treatment and control groups. The study by Cullen et al did also show that the
greatest effect in improving fever and mortality in their patient population was found in patients receiving a first cycle of chemotherapy as opposed to later cycles.

In Bucaneve et al, EBM review and Jadad scoring (5 out of 5) give great confidence in the outcome of the trial. It should also be noted that NNT for prophylaxis of fever in this trial is the lowest of those reviewed which have a Jadad score >2. A major difference between the GIMEMA trial and the SIGNIFICANT trial was that in the former, prophylaxis with levofloxacin was commenced prior to chemotherapy initiation and continued until neutropenia was resolved, or until infection required additional antibiotic therapy. This likely changes the host flora prior to the onset of neutropenia which may prevent infection through decreased GNB load in the host. The study by Cullen et al administered levofloxacin prophylaxis at days 5, 8, or 14 (depending on the number of days in the cycle and chemotherapy regimen to be given), and continued it for seven days in every treatment patient. The other difference between these two trials is the definition of neutropenia, which is < 500 cells/µL in the trial by Cullen et al and <1000 cells/µL in the trial by Bucaneve et al. This discrepancy however, doesn’t play a particularly important role in comparing these two studies, as Cullen et al did not use their definition for neutropenia in determining prophylactic dosing or administration.

The two largest and most current trials reviewed here, give confidence to recommend the proposition that prevention of fever and mortality is improved with fluoroquinolone prophylaxis in neutropenic cancer patients being treated with chemotherapy.

A follow up analysis in the Journal of Clinical Oncology, used the SIGNIFICANT trial data and examined the benefit of prophylactic therapy with levofloxacin within specific subgroups. This article used the design and data collection
of the original SIGNIFICANT trial and therefore was reviewed similarly for EBM criteria and Jadad scoring, but came to more specific conclusions within the subgroups it analyzed. It was found that breast cancer and especially testicular cancer and SCLC did benefit specifically from prophylaxis with levofloxacin, while some NHL patients may have been disadvantaged by this treatment. These conclusions support previously discussed findings that as myelosuppression increases with more cytotoxic chemotherapy agents (such as etoposide used in testicular cancer and SCLC), that febrile episodes and mortality may be decreased with fluoroquinolone prophylaxis.

All statistical reviews are made more powerful through increasing the population size, and in this study the limitation of the date range to this decade excluded many earlier trials from the review. This decision was made to evaluate the most current information available, however, this precluded review of larger treatment populations. An increased number of studies may also have been included with search criteria inclusive of foreign languages and other types of trials. Randomized controlled trials were used here as the best presented evidence with the most weight of all trial types, but conclusions can be effected by inclusion of other study types that may be significant. Further limitations can be seen in the restriction to antibiotic class and oral route. Oral fluoroquinolones are the current standard for prophylaxis of neutropenic fever but other antibiotics and routes are also commonly used. It is recommended that further study be completed to broaden search criteria to include valid trials that may have been disregarded by the intentionally narrowed scope of this review.
Conclusion

A systematic review was performed that allowed for inclusion of six studies that would provide insight into the clinical question of prevention. Does fluoroquinolone prophylaxis prevent fever and mortality in neutropenic cancer patients being treated with chemotherapy? All trials included in the study came to the conclusion that fever incidence is decreased with fluoroquinolone prophylaxis in this population. Improvement in mortality was found in two trials, but sufficient weight is not given to these results due to quality and validity of one of these trials. After weighing results of EBM reviews, Jadad scoring, and conclusive findings of these studies, there is more evidence that prophylactic use of fluoroquinolones prevents fever and mortality in treatment groups compared to control groups, with the benefit increasing as severity of myelosuppression increases. According to this systematic review, prophylactic fluoroquinolone use for prevention of fever is recommended for all neutropenic cancer patients receiving chemotherapy. Increased inclusion criteria of future review or meta-analysis studies is recommended to improve the data set included. Further design and implementation of quality RCTs is as always, both helpful and recommended, and should focus on trends between severity of myelosuppression and severity of outcomes.
<table>
<thead>
<tr>
<th>Study Article</th>
<th>Year</th>
<th>Population</th>
<th>Cancer type</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Start criteria</th>
<th>End criteria</th>
<th>Fever definition</th>
<th>Neutropenia definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tjan-Heijnen VCG, et al. <em>Annals of Onc</em></td>
<td>2001</td>
<td>161 adults (16-69 yrs old)</td>
<td>Small cell lung cancer</td>
<td>Ciprofloxacin 750mg po bid plus roxithromycin 150mg po bid</td>
<td>Matching placebo</td>
<td>Day 4 of cycle</td>
<td>Day 13 of cycle or neutropenic fever requiring IV antibiotics</td>
<td>Oral ≥38.3 °C or &gt;38 °C twice in 12 hours</td>
<td>Neutrophils &lt; 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>Prentice HG, et al. <em>Br. J. Haematol.</em></td>
<td>2001</td>
<td>150 adults (≥18 yrs old)</td>
<td>Haematologic malignancy or pre BMT conditioning</td>
<td>Ciprofloxacin 500mg po bid plus Colistin 1.5-3.0MU bid</td>
<td>Neomycin 500mg po bid plus colistin 1.5-3.0MU bid</td>
<td>Unknown</td>
<td>ANC ≥ 1.0 x 10⁹/L, for maximum of 30 days, or fever requiring intravenous antibiotics</td>
<td>Temp ≥38 °C for at least 2 hours</td>
<td>ANC &lt; 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>Nenova IS, et al. <em>Folia Medica</em></td>
<td>2001</td>
<td>70 adults (&gt;15 yrs old)</td>
<td>Hematologic malignancy</td>
<td>Ciprofloxacin 1g daily (48.8% of patients). Also: pefloxacin, oxacillin, norfloxacin</td>
<td>Placebo</td>
<td>At onset of neutropenia</td>
<td>ANC &gt; 1.0 x 10⁹/L or fever requiring adequate antimicrobial treatment</td>
<td>Unknown</td>
<td>ANC &lt; 1.0 x 10⁹/L</td>
</tr>
<tr>
<td>Cullen M, et al. (SIGNIFICANT trial) <em>NEJM</em></td>
<td>2005</td>
<td>1565 adults (&gt;16 yrs old)</td>
<td>Solid tumors, lymphoma</td>
<td>Levofloxacin 500mg po daily</td>
<td>Matching placebo</td>
<td>Day 5, 8, or 14 depending on cycle days and regimen</td>
<td>After 7 consecutive days of treatment intervention</td>
<td>Core &gt;38 °C</td>
<td>ANC &lt; 500 cells/µL</td>
</tr>
<tr>
<td>Bucaneve G, et al. (GIMEMA trial) <em>NEJM</em></td>
<td>2005</td>
<td>760 adults</td>
<td>acute leukemia, solid tumors, lymphoma</td>
<td>Levofloxacin 500mg po daily</td>
<td>Identical-appearing placebo</td>
<td>1-3 days prior to chemotherapy</td>
<td>ANC &gt; 1000 cells/µL or fever requiring empiric antibiotics</td>
<td>Axillary &gt;38.5 °C or &gt;38 °C twice in 12 hours</td>
<td>ANC &lt; 1000 cells/µL</td>
</tr>
<tr>
<td>Cullen M, et al. (SIGNIFICANT trial) <em>JCO</em></td>
<td>2007</td>
<td>1565 adults (&gt;16 yrs old)</td>
<td>Solid tumors, lymphoma</td>
<td>Levofloxacin 500mg po daily</td>
<td>Matching placebo</td>
<td>Day 5, 8, or 14 depending on cycle days and regimen</td>
<td>After 7 consecutive days of treatment intervention</td>
<td>Core &gt;38 °C</td>
<td>ANC &lt; 500 cells/µL</td>
</tr>
</tbody>
</table>

**Table I:** Included studies and their design details.
<table>
<thead>
<tr>
<th>Study Article</th>
<th>Method of Randomization</th>
<th>Population at conclusion</th>
<th>Method of blinding</th>
<th>Similarity of groups</th>
<th>Treatment of Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tjan-Heijnen VCG, et al. 2001 Annals of Onc</td>
<td>Randomized - Minimization technique.</td>
<td>Complete - Table provided</td>
<td>Double-blind - Placebo with sealed roster, treatment pack assigned by data center</td>
<td>Similar - limited information given (no ( p ) values given in table 1)</td>
<td>Equal</td>
</tr>
<tr>
<td>Prentice HG, et al. 2001 Br. J. Haematol.</td>
<td>Randomized - Unknown</td>
<td>Accounted for, not explained</td>
<td>Unknown</td>
<td>Similar - according to available data (no ( p ) values given in table 1)</td>
<td>Equal</td>
</tr>
<tr>
<td>Nenova IS, et al. 2001 Folia Medica</td>
<td>Randomized - Open, unknown</td>
<td>Complete - Survival rates of all patients reported for months 1-100.</td>
<td>Patients blinded by placebo. Otherwise open study.</td>
<td>Possible differences in sex and type of malignancy between treatment and control groups (no ( p ) values given in table 1)</td>
<td>Equal</td>
</tr>
<tr>
<td>Cullen M, et al. (SIGNIFICANT trial) 2005 NEJM</td>
<td>Randomized - Computerized minimization algorithm</td>
<td>Complete - Table provided</td>
<td>Double-blind - Sealed coded randomization with placebo</td>
<td>Similar (no ( p ) values given in table 1)</td>
<td>Equal</td>
</tr>
<tr>
<td>Bucaneve G, et al. (GIMEMA trial) 2005 NEJM</td>
<td>Randomized - Computer-generated random-number program</td>
<td>Complete - Table provided</td>
<td>Double-blind - Placebo with blinded assignment and treatment evaluation</td>
<td>Similar (no ( p ) values given in table 1)</td>
<td>Equal</td>
</tr>
<tr>
<td>Cullen M, et al. (SIGNIFICANT trial) 2007 JCO</td>
<td>Randomized - Described in prior publication</td>
<td>Complete - Table in prior publication</td>
<td>Double-blind - Described in prior publication</td>
<td>Similar - Table in prior publication</td>
<td>Equal</td>
</tr>
</tbody>
</table>

*Table II: EBM review criteria outcomes.*
<table>
<thead>
<tr>
<th>Study Article</th>
<th>Relative Risk</th>
<th>Relative Risk Reduction</th>
<th>Absolute Risk Reduction</th>
<th>Number Needed to Treat</th>
<th>Precision (95% CI)</th>
<th>Jadad Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tjan-Heijnen VCG, et al. 2001 <em>Annals of Onc</em></td>
<td>Fever: 0.56</td>
<td>Fever: 0.44</td>
<td>Fever: 0.19</td>
<td>Fever: 5.3</td>
<td>Unknown (Fever: $p = 0.007$ Death: $p = 0.022$)</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Death: 0.0</td>
<td>Death: 1.0</td>
<td>Death: 0.06</td>
<td>Death: 16.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prentice HG, et al. 2001 <em>Br. J. Haematol.</em></td>
<td>Fever: 0.81</td>
<td>Fever: 0.19</td>
<td>Fever: 0.17</td>
<td>Fever: 5.9</td>
<td>Unknown (Fever: $p = 0.02$)</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Death: 0.37</td>
<td>Death: 0.63</td>
<td>Death: 0.017</td>
<td>Death: 58.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nenova IS, et al. 2001 <em>Folia Medica</em></td>
<td>Infection: 0.19</td>
<td>Infection: 0.81</td>
<td>Infection: 0.32</td>
<td>Infection: 3.1</td>
<td>Unknown (Infection: $p &lt; 0.001$ Death in 1st month: $p &lt; 0.01$)</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Death in first month: 0.21</td>
<td>Death in 1st month: 0.79</td>
<td>Death in 1st month: 0.22</td>
<td>Death in 1st month: 4.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cullen M, et al. (SIGNIFICANT trial) 2005 <em>NEJM</em></td>
<td>First cycle-</td>
<td>First cycle-</td>
<td>First cycle-</td>
<td>First cycle-</td>
<td>First cycle-</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Fever: 0.44</td>
<td>Fever: 0.55</td>
<td>Fever: 0.044</td>
<td>Fever: 0.28 to 0.68</td>
<td>Fever: -0.26 to -0.14</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Severe infection or Death: 0.50</td>
<td>Severe infection or Death: 0.50</td>
<td>Severe infection or Death: 0.01</td>
<td>Severe infection or Death: 0.22 to 1.17</td>
<td>Death: -0.05 to 0.005</td>
<td></td>
</tr>
<tr>
<td>Bucaneve G, et al. (GIMEA trial) 2005 <em>NEJM</em></td>
<td>Fever: 0.76</td>
<td>Fever: 0.235</td>
<td>Fever: 0.20</td>
<td>Fever: 5</td>
<td>Fever: 0.26 to 0.79</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Death: 0.60</td>
<td>Death: 0.40</td>
<td>Death: 0.02</td>
<td>Death: 50</td>
<td>Testicular CA: 0.17 to 0.90</td>
<td></td>
</tr>
<tr>
<td>Cullen M, et al. (SIGNIFICANT trial) 2007 <em>JCO</em></td>
<td>Data unavailable for calculation</td>
<td>Data unavailable for calculation</td>
<td>Breast CA: 32</td>
<td>(NNT given for fever in first cycle)</td>
<td>Breast CA: 0.09 to 0.79</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Testicular CA: 0.39</td>
<td>Breast CA: 10</td>
<td>Testicular CA: 0.17 to 0.90</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SCLC: 0.09</td>
<td>SCLC: 0.09</td>
<td>SCLC: 0.01 to 0.73</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NHL: 0.55</td>
<td>NHL: 0.55</td>
<td>NHL: 0.38 to 5.17</td>
<td></td>
</tr>
</tbody>
</table>

*Table III: EBM review calculations and Jadad scores.*
References


