

Antibiotic Prophylaxis for Chemotherapy-Induced Febrile Neutropenia in Hematologic and Solid Organ Malignancies

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Abstract

Background and Objective: Febrile neutropenia (FN) frequently develops among cancer patients receiving chemotherapy and is associated with significant morbidity and mortality. Although the use of empiric antibiotics has been a standard of care for FN according to the last 2010 Infectious Disease Society of America (IDSA) guidelines, the role of prophylactic antibiotics in patients with high risk features in preventing febrile neutropenia remains to be elucidated. This study aims to investigate the role of antibiotic prophylaxis in preventing post-chemotherapy FN among patients with hematologic and solid organ malignancies.

Methods: A literature search of published English language clinical trials was performed using PubMed, MEDLINE, and the Cochrane Collaboration from January 1980 – October 2015. Four hundred thirty two articles were extracted from our literature search and narrowed down through specified inclusion and exclusion criteria. Results were analyzed based on 1) incidence of FN in post chemotherapy cancer patients, 2) mortality rate, and 3) incidence of FN with different antibiotics. Assessment of methodological quality of each study was done using the

Jadad scale. Odds ratios and Forest plots were computed and generated respectively using RevMan 5.2 (© 2013 the Cochrane Collaboration).

Results: Antibiotic prophylaxis reduced the incidence of FN (OR 0.59(0.37, 0.91)). Overall effect was significant; $Z = 2.35$ ($p = 0.02$). Febrile episodes occurred less frequently in those patients who received prophylactic antibiotic treatment (OR 0.43 (0.34, 0.53)) $Z = 7.59$ ($p < 0.00001$). The combined results in this sub-analysis on different antibiotic regimens used demonstrated that prophylaxis in general prevented FN by up to 3.51-fold among cancer patients who received chemotherapy, OR 3.51(3.10, 3.98). Results were statistically significant at $Z = 19.68$, $p < 0.00001$.

Conclusion: Antibiotic prophylaxis reduces the incidence of FN among cancer patients treated with cytotoxic chemotherapy, decreases febrile episodes in neutropenic patients, and overall, prevented FN by up to 3.51-fold.

Keywords: antibiotic prophylaxis, febrile neutropenia, chemotherapy, cancer

Introduction

In recent years, there has been an increasing rate of mortalities associated with febrile neutropenia and bacterial infections among cancer patients who receive chemotherapy. Worldwide, the incidence of chemotherapy-induced febrile neutropenia averages at approximately 2% (19.4 per 1000 oncology admissions) with a mortality rate of 12.5% among solid tumors.¹⁻³ Morbidity and mortality due to serious opportunistic infections in these immunocompromised patients have increased in recent years and have become a growing concern in oncology and infectious disease care. Hence, numerous studies on antibiotic prophylaxis for cancer patients with chemotherapy-induced neutropenia have emerged but often with conflicting conclusions and recommendations on its benefits. The plethora of evidence

on this matter has mostly concluded that antibiotic prophylaxis reduces mortality, febrile episodes, and bacterial infections in this subset of patients.⁴ Earlier research has elucidated on the use of fluoroquinolones as prophylaxis due to its good gram negative bacterial coverage, including *Pseudomonas aeruginosa*, while trimethoprim-sulfamethoxazole has been recommended for its high efficacy in the prevention of *Pneumocystis carinii* pneumonia according to the most recent 2010 IDSA guidelines.⁵ However, inadvertent use of these antibiotics often have serious health implications, such as potential adverse drug reactions associated with sulfamethoxazole or the emergence of quinolone-resistant gram negative bacilli with fluoroquinolones, thereby, limiting their use as prophylaxis.⁶ In fact, in the same guideline, antibiotic prophylaxis is not recommended for neutropenia since a reduction in mortality has not been clearly demonstrated alongside the growing concern of antibiotic resistance. It nevertheless recommends its use as empiric instead of prophylactic treatment.

The researcher therefore intended to create a meta-analysis which includes the most recent investigations not previously used in a recent meta-analysis, in order to assess the current status of antibiotic prophylaxis, to determine

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whether it has a role in preventing febrile neutropenia and its complications.

Methods

Eligibility criteria

Abstracts of all citations and retrieved studies were reviewed. The following criteria were used to include published studies: (1) studies evaluating the role of antibiotic prophylaxis in febrile neutropenic cancer patients, (2) studies which compared combination treatment with granulocyte colony-stimulating factor (G-CSF) and an antibiotic versus G-CSF alone for febrile neutropenia, (3) parameters measured include all-cause mortality, hospital stay, and documented bacterial infections (4) randomized controlled trials (RCT) and prospective trials designed studies.

Articles were excluded if one of the following existed: (1) participants with neutropenia not induced by chemotherapy (2) there was insufficient information for extraction of data (3) non-English articles, (4) unpublished results.

Literature search strategy

A literature search of published English language clinical trials was performed using PubMed, MEDLINE, and the Cochrane Collaboration Library from January 1980 – October 2013 on the role of antibiotic prophylaxis for febrile neutropenic cancer patients. The following keywords were used: “antibiotic prophylaxis” and “febrile neutropenia”. All matches were appraised by titles and those relevant to the study were initially included for the appraisal. Full articles were initially retrieved and those with missing or unpublished data were excluded. A total of 432 studies or matches were identified in the preliminary search which was subsequently narrowed down through filters. We selected full text articles on human adult subjects thereby narrowing down the matches to a total of 156 articles which were screened through titles and abstracts. Out of the 156 articles, 22 were retrieved and appraised based on the inclusion and exclusion criteria previously set. From the 22 studies, nine were then excluded after appraisal; one article was in French, another in Italian, and a third was in Spanish, the other excluded articles were either Reviews, correspondences or commentaries on previous Reviews. The remaining 13 articles were assessed for eligibility leaving seven articles included in the quantitative analysis. Risk of bias and validity of each retrieved article was addressed and graded using the the Jadad scoring system.

We reviewed trials evaluating the effectiveness of antibiotic prophylaxis in preventing mortalities among chemotherapy induced febrile neutropenic cancer patients. Data sources included RCTs and prospective trials published between January 1980 to October 2013, as described previously (keywords: *antibiotic prophylaxis*,

febrile neutropenia).

All data were extracted by the researcher (RMM, AAL) according to the inclusion criteria listed above. Analysis was checked by two independent advisers (CLA, EVR). Subject demographics were compared and checked for homogeneity (Table I). The following characteristics were also collected from each study: first author, year of publication, country of the first or corresponding author, number of cases and controls, matching criterias, cancer type, and antibiotic used (Table II).

Statistical analysis

The meta-analyses evaluated the effectiveness of antibiotic prophylaxis in preventing mortality and improving outcomes among chemotherapy-induced febrile neutropenic patients. Effect estimates for odds ratio (OR) were used to determine statistical difference in mortality, occurrence of febrile neutropenia, and its incidence despite the use of different antibiotics. Results and figures were derived from RevMan 5.2 (© 2013 the Cochrane Collaboration) and computed with the fixed-effects models. All statistical tests were 2-sided and effect estimates were deemed statistically significant when $P \leq .05$.

Results

Twenty two trials were evaluated for eligibility and thirteen were included in this analysis. Figure 1 shows the reasons for exclusion. Seven out of the thirteen studies were included while six were further excluded from the analysis. The population consisted of a total of 3253 patients fulfilling the inclusion criteria, 1655 were females and 1598 were males. The mean age of the entire population in study was computed to be 52.825 years. The meta-analysis included patients with different types of tumors, majority consisted of hematologic malignancies. These patients were subjected to different cytotoxic chemotherapy regimen (CDE: Cyclophosphamide, Doxorubicin, Etoposide; FEC: Fluorouracil, epirubicin, cyclophosphamide; AC: Doxorubicin and cyclophosphamide; BEP: Bleomycin, etoposide, and cisplatin; EP: etoposide and cisplatin; PE: platin and etoposide; CAV: cyclophosphamide, doxorubicin, and vincristine; CAVE: cyclophosphamide, doxorubicin, vincristine and etoposide; CHOP: cyclophosphamide, doxorubicin, vincristine, and prednisolone; ABVD: doxorubicin, bleomycin, vinblastine, dacarbazine).

Characteristics of the included trials

Studies included in this meta-analysis consisted mostly of RCTs and one prospective observational study done in different centers worldwide (Table II). These studies were matched against each other and compared using criteria such as antibiotic prophylaxis use, cancer patients who previously underwent cytotoxic

chemotherapy with significant risk for profound neutropenia. There was good homogeneity among the sample population which included patients with different types of cancer but mostly those with hematologic tumors. All patients in the population had, at one time, received cytotoxic chemotherapy.

Six out of seven included studies were RCTs on antibiotic prophylaxis for prevention of chemotherapy induced febrile neutropenia. Two trials included only small cell lung cancer (SCLC patients). Two other trials included undefined hematologic cancers, while the remaining two trials consisted mostly of a good mix of different types of cancer.^{3, 6-11}

Figure 2. Search strategy flowchart.

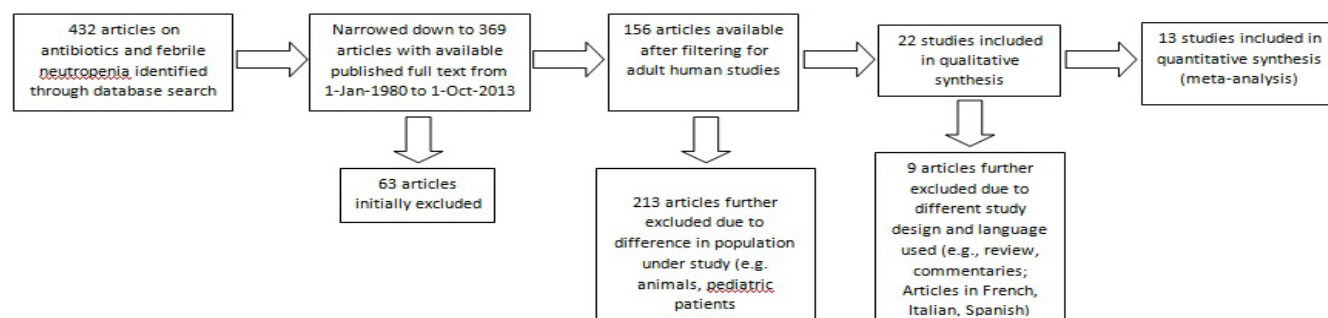


Table I. Demographics

Authors	N	Age (mean)	Males	Females	Type of tumor	Regimen	Treatment
Feld et al (2000)	409	48.45	217	192	Hematologic	***	Meropenem Ceftazidime
Tjan-Heijnen et al (2001)	161	60.25	120	41	SCLC	CDE	Ciprofloxacin + Roxithromycin Placebo
Garnica et al (2004)	220	40.5	136	84	Hematologic	***	Ciprofloxacin Placebo
Bucaneve et al (2005)	675	48.25	370	305	Acute leukemia Lymphoma Hodgkin's Solid Other hematologic	***	Levofloxacin Placebo
Cullen et al (2005)	1565	***	692	873	Breast Testicular SCLC NHL Hodgkin's	FEC, AC BEP, EP PE, CAVE CHOP ABVD	Levofloxacin Placebo
Timmer-Bonte et al (2005)	175	64	113	62	SCLC	CDE	Ciprofloxacin + Roxithromycin AB+GCSF
Lalami et al (2013)	48	55.5	7	41	Solid	(see paper)	Ciprofloxacin + Amoxicillin/Clavulanate AB+GCSF

*** Data not reported

Table II. Characteristics of included trials

Authors	Year	Design	Country	No. of cases	No. of control	Treatment protocols	Matching Criteria	ITT
Feld et al	2000	Randomized double-blind trial	Canada & USA	N/A	N/A	Undefined chemotherapy protocol	Antibiotic prophylaxis, Cancer patients with prior undefined chemotherapy protocol at high risk of developing neutropenia	N
Tjan-Heijnen et al	2001	Double-blind placebo-controlled phase III study	Belgium	83	80	CDE+GCSF,	Antibiotic prophylaxis, placebo, Cancer patients with prior chemotherapy and assessed with neutropenia	N
Garnica et al	2004	Prospective observational study	Brazil	219	110	Undefined chemotherapy protocol	Antibiotic prophylaxis, placebo, Cancer patients with prior chemotherapy and assessed with neutropenia	Y
Bucaneve et al	2005	Prospective, multi-center, double-blind, randomized, placebo-controlled trial	Italy	339	336	Chemotherapeutic protocol undefined	Antibiotic prophylaxis, placebo, Cancer patients with prior chemotherapy at high risk of developing neutropenia	Y
Cullen et al	2005	Randomized, double-blind, placebo-controlled trial	UK	781	784	Cytotoxic chemotherapy protocol undefined	Antibiotic prophylaxis, placebo, Cancer patients on chemotherapy at high risk of developing neutropenia	Y
Timmer-Bonte et al	2005	Randomized Phase III trial	The Netherlands	85	Solid	(see paper)	Ciprofloxacin + Amoxicillin/Clavulanate AB+GCSF	
Lalami et al	2013	Prospective randomized study	Belgium	25	23	Undefined chemotherapy protocol	Antibiotic prophylaxis, GCSF, Cancer patients with prior chemotherapy and assessed with neutropenia	N

Assessment of Methodological Quality

The Jadad scoring system was introduced in 1996 by Alejandro Jadad and has been used as the gold standard in assessing the methodological quality of studies. This validated score lies in the range of 0-5 and studies are scored according to three main criteria: Randomization, blinding, and accountability of all patients, including withdrawals. Studies are rated as high quality if they receive a Jadad

score of 4 or 5, or low quality if equal to or less than three.¹² In our investigation, six out of seven appraised articles were rated as high quality based on the Jadad score (Table III). The article of Garnica et al. was included because of comparable data which was found valuable in the analysis on mortality rates and febrile episodes.

Table III. Jadad Scoring for the appraised articles.

JADAD Scoring	Feld et al	Tjan-Heijnen et al	Garnica et al	Bucaneve et al	Cullen et al	Timmer-Bonte et al	Lalami et al
Was the study described as randomized?	+1	+1	0	+1	+1	+1	+1
Was the method used to generate the sequence of randomisation described and appropriate?	+1	+1	0	+1	+1	+1	+1
Was the study described as double blind?	+1	+1	0	+1	+1	0	+1
Was the method of double blinding described and appropriate?	+1	+1	0	+1	+1	0	+1
Was there a description of withdrawals and dropouts?	0	0	0	+1	+1	+1	0
Deduct one point if the method used to generate the sequence of randomisation was described and it was inappropriate.	+1	+1	0	+1	+1	+1	+1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate.	+1	+1	0	+1	+1	0	+1
Total	+6	+6	0	+7	+7	+4	+6

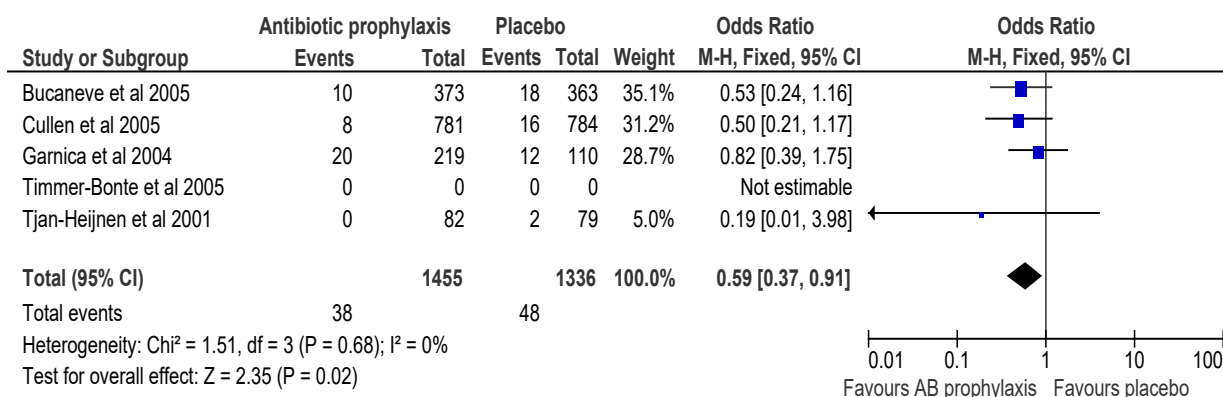
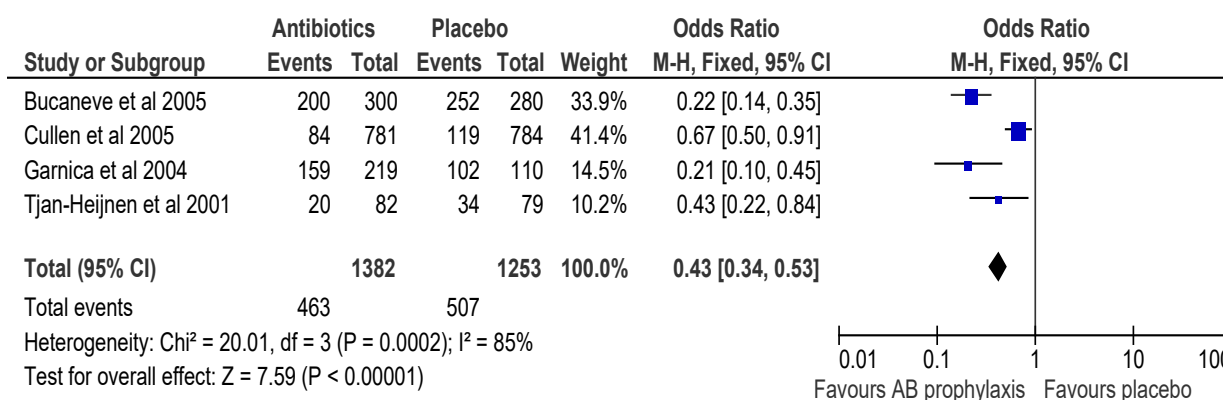
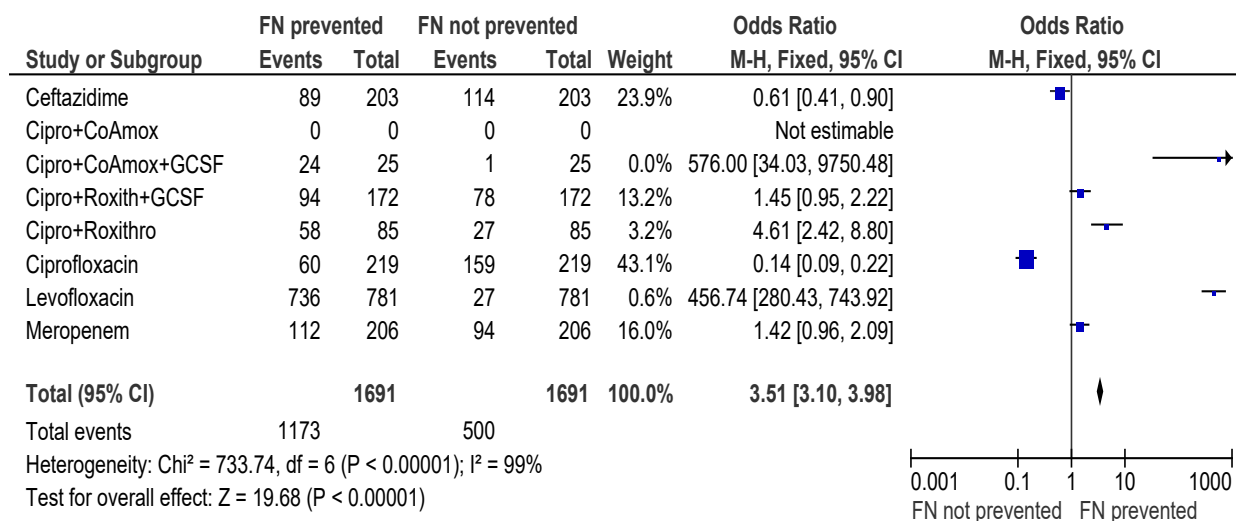
Figure 2. All-cause mortality with antibiotic prophylaxis versus placebo.**Figure 3.** Febrile episodes with antibiotic prophylaxis versus placebo

Figure 4. Antibiotic regimens for prevention of febrile neutropenia compared

Quantitative Results of the Meta-Analysis

We analyzed the results of trials with mortality data and compared the overall effect estimate and found that treatment with antibiotic prophylaxis reduced the risk of febrile neutropenia with a low likelihood of 0.59 (odds ratio) CI (0.37, 0.91). Overall effect was statistically significant; $Z = 2.35$ ($p = 0.02$). Similarly, febrile episodes in four included studies also showed similar trends with antibiotic prophylaxis, overall OR (0.43 (0.34, 0.53)). Febrile episodes were also found to occur less frequently in those with prophylactic treatment with a very statistically significant Z value of 7.59 ($p < 0.00001$). Finally, the different antibiotics used whether alone, in combination with another antibiotic, or with addition of GCSF were compared against each regimen to determine which had the most beneficial effect. We found that quinolones, specifically, levofloxacin resulted to better outcomes in terms of FN prevention in all the studies analyzed with an overall odds ratio of 456.74, in favor of prophylaxis with levofloxacin. The combined results in this sub-analysis demonstrates that antibiotic prophylaxis in general is able to increase FN prevention by up to 3.51-fold among cancer patients who received cytotoxic chemotherapy, OR 3.51 (3.10, 3.98). The results were statistically significant at $Z = 19.68$, $p < 0.00001$.

Discussion

Numerous trials have emerged in recent years investigating on the potential role of antibiotic prophylaxis for neutropenic cancer patients who have received cytotoxic chemotherapy in order to prevent serious complications such as febrile neutropenia, or much worse, sepsis secondary to bacterial infections. However, results have remained inconclusive. Majority of RCTs on this topic have proven significant advantage versus placebo, while

a minority showed no actual benefit over placebo. Our results have largely been in favor of antibiotic prophylaxis since it has demonstrated clear advantage in reducing all-cause mortality (0.59(0.37-0.59)) and preventing fever onset (0.43(0.34-0.53)) better than placebo. Furthermore, evaluation of the efficacy of different antibiotic regimen also demonstrated benefits in preventing febrile neutropenia especially with levofloxacin as prophylaxis. Overall odds ratio showed that antibiotic prophylaxis was able to prevent febrile neutropenia by 3.51-fold among patients who received cytotoxic chemotherapy either for hematologic or solid organ malignancies.

The seemingly favorable results, however, should also be analyzed under the context of antimicrobial stewardship. It is ideal to include in the analysis a comparison on the reported adverse effects and rates of resistance to antibiotics among patients receiving prophylaxis. We reviewed our appraisal of the included studies and found that only one trial by Bucaneve et al in 2005 included an analysis on resistance rates to levofloxacin in their study population. They found that 41 out of 47 or 87.23% of those patients who received antibiotic prophylaxis had developed antibiotic resistance in contrast to only 51.47% in the placebo group.¹³ This elucidates the need for further subanalysis on this matter since antibiotic resistance is a continuously growing medical concern brought about by the emergence of multi-drug resistant organisms. Furthermore, only the study by Cullen and associates had a subanalysis comparing the efficacy of levofloxacin in preventing febrile neutropenia between solid tumors and leukemias. They found that patients with acute leukemia had more sustained neutropenia (19 days with a neutrophil count of no more than 1000 per cubic millimeter) and more profound neutropenia (11 days with a neutrophil count of no more than 100 per cubic millimeter) yet the overall efficacy was similar in the two subgroups.⁹

Conclusion

Febrile neutropenia is a common cause of morbidity among cancer patients undergoing cytotoxic chemotherapy and there has been no clear recommendations regarding antibiotic prophylaxis to prevent its occurrence in the light of the principle of antimicrobial stewardship in an era of growing antibiotic resistance. It is evident in the analysis that prophylactic antibiotic use should be advocated since it reduces the risk of FN in this subset of patients though prudent risk-stratification should be done beforehand. Fluoroquinolones particularly, levofloxacin remains to have good results in preventing FN compared to other antibiotics.

Limitations and Recommendations

Our investigation only included published full text articles in the English language retrieved through an online database search and is limited to comparable variables reported in the studies included. As mentioned above, our study did not include a comparison on resistance rates to antibiotics. We recommend therefore, a more thorough database search to include both published and unpublished studies to decrease the possibility of publication bias and to address the file drawer problem. Second, an online translation or hired translators are recommended for qualified studies published in non-English language that may allow us to include notable trials for evaluation. Lastly, further study on rates of resistance to the common antibiotics being used for prophylaxis is highly recommended as this will greatly affect our management decision.

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