

## ORIGINAL ARTICLE

# Antibacterial Prophylaxis after Chemotherapy for Solid Tumors and Lymphomas

Michael Cullen, M.D., Neil Steven, Ph.D., Lucinda Billingham, Ph.D., Claire Gaunt, B.Sc., Mark Hastings, M.D., Peter Simmonds, M.D., Nicholas Stuart, M.D., Daniel Rea, Ph.D., Mark Bower, Ph.D., Indrajit Fernando, M.D., Robert Huddart, Ph.D., Simon Gollins, D.Phil., and Andrew Stanley, M.R.Pharm.S., for the Simple Investigation in Neutropenic Individuals of the Frequency of Infection after Chemotherapy +/- Antibiotic in a Number of Tumours (SIGNIFICANT) Trial Group\*

## ABSTRACT

From University Hospital Birmingham Cancer Centre, Birmingham (M.C., I.F.); Ysbyty Gwynedd, Bangor (N.S.); Cancer Research UK Institute for Cancer Studies, University of Birmingham, Birmingham (N.S., L.B., C.G., D.R.); the National Public Health Service Wales, Microbiology, Cardiff (M.H.); Royal South Hampshire Hospital, Southampton (P.S.); Glan Clwyd, Rhyl (S.G.); Chelsea and Westminster Hospital, London (M.B.); Royal Marsden Hospital, London (R.H.); and City Hospital, Birmingham (A.S.) — all in the United Kingdom. Address reprint requests to Dr. Cullen at University Hospital Birmingham NHS Foundation Trust, Birmingham B15 2TH, United Kingdom, or at michael.cullen@uhb.nhs.uk.

\*The other members of the SIGNIFICANT Trial Group are listed in the Appendix.

N Engl J Med 2005;353:988-98.  
Copyright © 2005 Massachusetts Medical Society.

**BACKGROUND**

The role of prophylactic antibacterial agents after chemotherapy remains controversial.

**METHODS**

We conducted a randomized, double-blind, placebo-controlled trial in patients who were receiving cyclic chemotherapy for solid tumors or lymphoma and who were at risk for temporary, severe neutropenia (fewer than 500 neutrophils per cubic millimeter). Patients were randomly assigned to receive either 500 mg of levofloxacin once daily or matching placebo for seven days during the expected neutropenic period. The primary outcome was the incidence of clinically documented febrile episodes (temperature of more than 38°C) attributed to infection. Secondary outcomes included the incidence of all probable infections, severe infections, and hospitalization but did not include a systematic evaluation of antibacterial resistance.

**RESULTS**

A total of 1565 patients underwent randomization (784 to placebo and 781 to levofloxacin). The tumors included breast cancer (35.4 percent), lung cancer (22.5 percent), testicular cancer (14.4 percent), and lymphoma (12.8 percent). During the first cycle of chemotherapy, 3.5 percent of patients in the levofloxacin group had at least one febrile episode, as compared with 7.9 percent in the placebo group ( $P < 0.001$ ). During the entire chemotherapy course, 10.8 percent of patients in the levofloxacin group had at least one febrile episode, as compared with 15.2 percent of patients in the placebo group ( $P = 0.01$ ); the respective rates of probable infection were 34.2 percent and 41.5 percent ( $P = 0.004$ ). Hospitalization was required for the treatment of infection in 15.7 percent of patients in the levofloxacin group and 21.6 percent of patients in the placebo group ( $P = 0.004$ ). The respective rate of severe infection was 1.0 percent and 2.0 percent ( $P = 0.15$ ), with four infection-related deaths in each group. An organism was isolated in 9.2 percent of probable infections.

**CONCLUSIONS**

Among patients receiving chemotherapy for solid tumors or lymphoma, the prophylactic use of levofloxacin reduces the incidence of fever, probable infection, and hospitalization.

**B**ACTERIAL INFECTIONS AMONG patients receiving myelosuppressive chemotherapy for solid cancers and lymphomas lead to complications, hospitalization, the use of major resources,<sup>1</sup> delays and dose reductions in chemotherapy regimens,<sup>2</sup> and in some cases, death. Guidelines have generally advised against the routine use of antibiotics for prophylaxis,<sup>3-5</sup> but a recent survey of 3600 physicians in the United States revealed that 45 percent routinely use fluoroquinolone prophylaxis in patients receiving chemotherapy.<sup>6</sup> Uncertainty about the prophylactic use of antibiotics continues despite decades of controversy and investigation.<sup>7,8</sup> Meta-analysis of nine trials (involving 731 patients) comparing fluoroquinolone prophylaxis with no prophylaxis demonstrated significant reductions in a number of outcomes of infection.<sup>9</sup> However, when blinded trials alone were analyzed, there was no reduction in the incidence of fever, and seven trials did not analyze data on an intention-to-treat basis. Finally, most trials focused on in-patient care of patients with leukemia; patients with solid tumors who were receiving standard-dose chemotherapy were included in only three of the nine trials.

Meta-analyses have indicated that fluoroquinolones are more likely than trimethoprim-sulfamethoxazole to have prophylactic efficacy and that the addition of a penicillin or macrolide antibiotic does not further reduce the incidence of febrile episodes.<sup>9,10</sup> Levofloxacin is an agent with an acceptable side-effect profile that is administered once daily, thus optimizing compliance, a major issue in prophylaxis. It is active against a wide range of gram-negative pathogens, as well as some gram-positive bacteria and organisms causing atypical pneumonias.<sup>11</sup> We conducted a large, randomized, double-blind, placebo-controlled trial designed to determine the efficacy of an empirical strategy, offering seven days' prophylaxis with levofloxacin during the period of anticipated neutropenia in patients with solid cancers or lymphomas who were considered at risk for infection during cyclic, myelosuppressive chemotherapy.

---

## METHODS

---

### PATIENTS

Oncology or hematology specialists throughout the United Kingdom who were treating patients for cancer were invited to participate in the trial. Adults (defined as those at least 16 years of age) commencing

cytotoxic chemotherapy for solid tumors or lymphoma and at risk for bacterial infection were randomly assigned to receive levofloxacin or matching placebo for seven days to cover the period of anticipated neutropenia. The protocol listed widely used chemotherapy regimens and doses associated with a known risk of cyclic severe neutropenia (fewer than 500 neutrophils per cubic millimeter) but that were not routinely given with granulocyte colony-stimulating factor (G-CSF) or stem-cell support. Patients remained enrolled in the trial for up to six cycles of chemotherapy. A cycle of chemotherapy was defined as the standard, minimal duration of a particular regimen between the start of one treatment and the next that was sufficient to allow recovery from acute adverse effects, including myelosuppression. Exclusion criteria at the time of randomization were active infection, current antibacterial therapy, planned use of G-CSF, a history of adverse reactions to fluoroquinolones, epilepsy, a creatinine clearance below 40 ml per minute, pregnancy, and breast-feeding.

All patients gave written informed consent, and the research was approved by the ethics committee of each participating institution. The commercial sponsor played no role in the design of the trial, recruitment, data collection, analysis, or writing of the manuscript.

### RANDOMIZATION

Randomization involved the use of a computerized minimization algorithm, which was developed and kept securely by the Cancer Research UK Clinical Trials Unit, Birmingham, and was accessed by participating investigators by means of the telephone. Patients were stratified according to age (less than 40 years, 40 to 59 years, or 60 years or older), the type of cancer (breast cancer, testicular cancer, small-cell lung cancer, non-Hodgkin's lymphoma, Hodgkin's disease, or other), and treatment center. The following baseline variables potentially related to the risk of infection were recorded at randomization: World Health Organization (WHO) performance status, adjuvant use of chemotherapy, presence of a long-term indwelling venous catheter, and previous myelosuppressive chemotherapy or previous radiotherapy likely to compromise bone marrow function.

### OUTCOME MEASURES

The primary outcome measure was the incidence of clinically documented febrile episodes, defined by a core temperature exceeding 38°C, attributed to in-

fection. The incidence of all probable infections was a secondary outcome measure. Probable infections were defined by at least one of the following: a clinically documented febrile episode; other signs attributed to a systemic response to infection, such as hypothermia (temperature below 35.6°C), low-grade fever (temperature, 37.5 to 37.9°C), tachycardia (more than 90 beats per minute), or tachypnea (more than 20 breaths per minute); signs of a focus of infection; or the use of antibacterial therapy. Physicians were required to report episodes that occurred during each chemotherapy cycle or within four weeks after the final cycle. The incidence of hospitalization for infection and the frequency of severe infection were further secondary outcome measures. Severe infections were defined by the presence of infection-related sepsis syndrome (i.e., infection causing hypotension with or without evidence of impaired organ perfusion), death from infection, or both.

Additional secondary outcomes included the site of infection and the neutrophil count at the onset of infection. Microbiologic outcomes included causative organisms isolated during infection. The clinical significance of isolates was assessed by a microbiologist who was unaware of patients' treatment assignments.

On the diagnosis of an episode of infection, patients were evaluated and treated according to clinical findings and local policy. Study medication was withdrawn for that cycle alone, but patients could remain in the trial for subsequent cycles if blinding had been maintained.

#### TRIAL MEDICATION

Trial medication consisted of 500-mg tablets of levofloxacin or matching placebo, supplied in single-use packs sufficient for six cycles and identified only by a unique number. The tablets were dispensed one cycle at a time to be taken once daily for seven consecutive days just before and during the anticipated period of neutropenia. Treatment began on day 8 for 14-day and 21-day cycles, on day 5 for regimens associated with an early onset of neutropenia (e.g., docetaxel), and on day 15 for 28-day cycles. To facilitate compliance monitoring, patients reported the number of tablets taken with each cycle, and the trial-medication bottles were returned to the pharmacy for pill counts after each cycle.

The host pharmacy was allowed to break the code in the event of a serious adverse event attributed to the study drug or a serious infection for which

this knowledge was deemed essential to guide antibacterial therapy. Unblinding was not offered routinely in the event of a febrile episode. Instead, patients continued to take the assigned drug during subsequent cycles.

The study drug was permanently discontinued if the physician believed antibacterial prophylaxis was definitely indicated, if unblinding was required, or if an adverse event occurred that was attributed to the study drug and thus warranted its discontinuation. If the study drug was discontinued before the completion of the planned number of chemotherapy cycles, monitoring for outcome measures continued for up to six cycles to allow the inclusion of the patient in an intention-to-treat analysis.

#### STATISTICAL ANALYSIS

We estimated that we would need to enroll 1500 patients for the study to have a statistical power of 80 percent to detect a halving of the rate of febrile episodes in the first cycle in the levofloxacin group, as compared with the placebo group, and a power of 90 percent to detect a one-third reduction in the cumulative rate of febrile episodes during all cycles, given a significance level of 5 percent. Rates of febrile episodes, all probable infections (including febrile episodes), hospitalization for infection, and severe infections per patient were compared with the use of continuity-adjusted chi-square tests. The analysis was carried out on an intention-to-treat basis, with all patients included in their assigned treatment groups and the small numbers of patients with an unknown outcome (which were similar in the two groups) combined with those who had no events. A sensitivity analysis confirmed the validity of this assumption.

The relative differences between the treatment groups were expressed as relative risks with 95 percent confidence intervals. Data on secondary outcomes relating only to cycles with infection are presented descriptively.

---

#### RESULTS

---

From August 1999 to April 2003, 1565 patients from 60 centers underwent randomization, 784 to placebo and 781 to levofloxacin (Fig. 1). Three patients in each group were ineligible but were included in the intention-to-treat analysis. A total of 90.5 percent of patients had a WHO performance status of 0 or 1, and nearly half were treated in the adjuvant context. About one third of the patients had

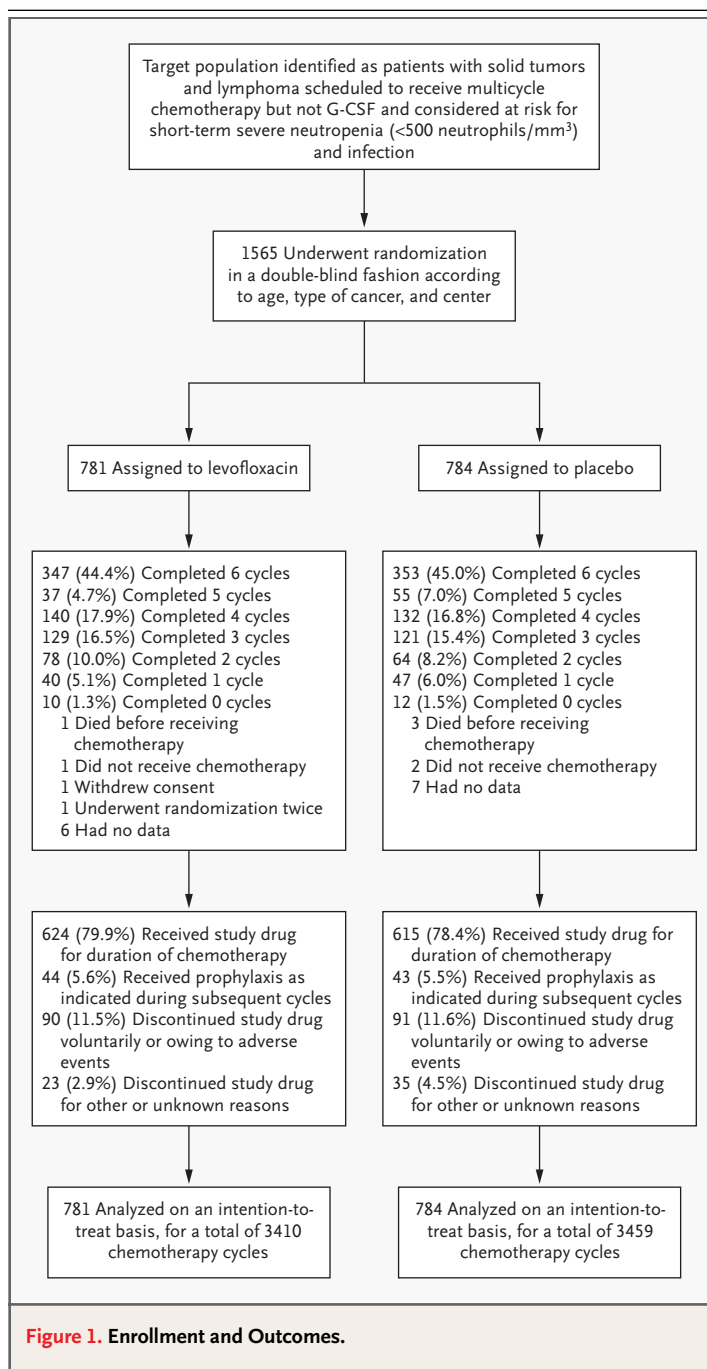
breast cancer, but substantial numbers were treated for testicular and small-cell lung cancers. The treatment groups were well balanced with respect to all baseline characteristics and risk factors (Table 1). A total of 6869 cycles were analyzed. The number of cycles studied and the numbers of patients with missing data were similar in the two groups (Fig. 1).

#### INFECTION

Of the 1565 randomized patients, 203 (13.0 percent) had at least one febrile episode, and there were 248 febrile episodes in total (3.6 percent of cycles). At least 1 probable infection occurred in 592 patients (37.8 percent), and there were a total of 817 probable infections (11.9 percent of cycles) (Table 2).

A clinically documented febrile episode occurred during the first chemotherapy cycle in 27 of 781 patients in the levofloxacin group (3.5 percent), as compared with 62 of 784 patients in the placebo group (7.9 percent) (Table 3). The relative risk of a clinically documented febrile episode was 0.44 (95 percent confidence interval, 0.28 to 0.68;  $P < 0.001$ ), indicating a 56 percent reduction in the risk of fever during the first cycle with the use of levofloxacin therapy, as compared with placebo. There was also a significant reduction in the incidence of the more inclusive category of probable infections with levofloxacin prophylaxis, as compared with placebo, resulting in a 28 percent reduction in the risk during the first cycle of chemotherapy (relative risk, 0.72; 95 percent confidence interval, 0.57 to 0.90;  $P = 0.005$ ).

Events related to infection in individual patients during multiple cycles are not independent: patient factors, changes in treatment, and possible bacterial resistance resulting from antibacterial treatment in an earlier cycle may influence the risk of infection and the effect of prophylaxis in subsequent cycles. For this reason, data obtained during the entire chemotherapy course were analyzed per patient rather than per cycle, and levofloxacin was found to confer a protective benefit similar to that identified in the analysis of the first cycle (Table 3). During the entire course of chemotherapy, 84 of 781 patients in the levofloxacin group had a clinically documented febrile episode (10.8 percent), as compared with 119 of 784 patients in the placebo group (15.2 percent). Prophylactic levofloxacin was thus associated with a 29 percent relative reduction in the risk of a febrile episode (relative risk, 0.71; 95 percent confidence interval, 0.55 to 0.92;  $P = 0.01$ )



and an 18 percent relative reduction in the risk of probable infection (relative risk, 0.82; 95 percent confidence interval, 0.73 to 0.94;  $P = 0.004$ ). Only 36 patients (2.3 percent) had more than one febrile episode, but the incidence of multiple fevers was more than halved among those receiving levofloxacin, as compared with those receiving placebo (10 vs. 26).

**Table 1. Baseline Characteristics of the Patients.\***

Characteristic	Levofloxacin (N=781)	Placebo (N=784)
Sex — no. (%)		
Male	338 (43.3)	354 (45.2)
Female	443 (56.7)	430 (54.8)
Age		
16–39 yr — no. (%)	157 (20.1)	147 (18.7)
40–59 yr — no. (%)	336 (43.0)	337 (43.0)
≥60 yr — no. (%)	288 (36.9)	300 (38.3)
Median — yr	55	55
Interquartile range — yr	42–63	43–65
Range — yr	18–82	16–83
WHO performance status		
0	493 (63.1)	477 (60.8)
1	213 (27.3)	234 (29.8)
2	65 (8.3)	56 (7.1)
3 or 4	9 (1.2)	16 (2.0)
Unknown	1 (0.1)	1 (0.1)
Type of cancer and most commonly used chemotherapy regimens — no. (%)		
Breast cancer †	275 (35.2)	279 (35.6)
FEC	109	116
AC	64	51
Testicular cancer	114 (14.6)	111 (14.2)
BEP	96	93
EP	14	14
Small-cell lung cancer	110 (14.1)	110 (14.0)
PE	50	45
CAV	14	19
CAVE	14	18
Non-Hodgkin's lymphoma	79 (10.1)	72 (9.2)
CHOP	74	63
Hodgkin's disease	24 (3.1)	25 (3.2)
ABVD	20	15
Other ‡	179 (22.9)	187 (23.8)
Chemotherapy being given in adjuvant setting — no. (%)§	354 (45.3)	335 (42.7)
Indwelling venous catheter present — no. (%)	59 (7.6)	70 (8.9)
Previous myelosuppressive chemotherapy given — no. (%)	73 (9.4)	88 (11.2)
Previous radiotherapy given — no. (%)¶	33 (4.2)	40 (5.1)

\* FEC denotes fluorouracil, epirubicin, and 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; and ABVD doxorubicin, bleomycin, vinblastine, and dacarbazine.

† A total of 206 patients in the placebo group and 212 patients in the levofloxacin group received adjuvant therapy.

‡ This category includes non–small-cell lung cancer in 132 patients, ovarian cancer in 54 patients, gastric cancer in 40 patients, esophageal cancer in 40 patients, bladder cancer in 28 patients, sarcoma in 14 patients, colorectal cancer in 12 patients, endometrial cancer in 10 patients, and cervical cancer, mesothelioma, pancreatic cancer, liver cancer, thymoma, kidney cancer, melanoma, peripheral neuroectoderm, prostate cancer, Merkel-cell cancer, myeloma, tonsillar cancer, multiple primary cancers, and unknown primary cancer in fewer than 10 patients each.

§ The status of two patients in each group was unknown.

¶ The status of one patient was unknown.

**Table 2. Characteristics of 817 Probable Infections among 6869 Cycles.**

Variable	Focus of Infection	No Focus of Infection	No./Total No. (% of Cycles)
	<i>no. of probable infections (% of total)</i>		
Sign of probable infection			
Fever	144 (17.6)	104 (12.7)	248/6869 (3.6)
Other systemic signs	184 (22.5)	56 (6.9)	240/6869 (3.5)
No systemic signs	298 (36.5)	31 (3.8)*	329/6869 (4.8)
Focus of infection			
Upper respiratory tract	197 (24.1)	—	
Lower respiratory tract	105 (12.9)	—	
Gastrointestinal tract and anal abscesses	36 (4.4)	—	
Urinary tract	68 (8.3)	—	
Skin and soft tissue	86 (10.5)		
Venous catheter	39 (4.8)	—	
Oral mucosa and teeth	41 (5.0)	—	
Multiple sites	36 (4.4)	—	
Other sites	17 (2.1)		
Unspecified	1 (0.1)		
No focus of infection	—	191 (23.4)	

\* In these 31 episodes, the only evidence of a probable infection was the reported use of antibacterial therapy in 18; no further data were available for the other 13 episodes.

#### HOSPITALIZATION FOR INFECTION

The reduction in the incidence of febrile episodes and probable infection associated with levofloxacin prophylaxis was reflected in a significant reduction in the percentage of patients hospitalized for infection (Table 3). There was a 36 percent reduction in the risk of hospitalization during cycle 1 with levofloxacin therapy, as compared with placebo (relative risk, 0.64; 95 percent confidence interval, 0.46 to 0.90;  $P=0.01$ ), and a 27 percent reduction across all cycles (relative risk, 0.73; 95 percent confidence interval, 0.59 to 0.90;  $P=0.004$ ).

#### SEVERE INFECTIONS

Severe infection, characterized by infection-related sepsis syndrome, death, or both, occurred in 8 patients in the levofloxacin group, as compared with 16 in the placebo group (1.0 percent vs. 2.0 percent,  $P=0.15$ ); 4 patients died in each group. The eight severe infections in the levofloxacin group (including those resulting in the four deaths) occurred outside the period in which the white-cell count was expected to be lowest or when the patients were not taking levofloxacin (because of a failure to prescribe the drug, the discontinuation of levofloxacin therapy,

or noncompliance with therapy). In comparison, 8 of the 16 severe infections in the placebo group, including those leading to three of four deaths, occurred during the expected nadir period while the patients were taking placebo.

#### TIMING OF INFECTIONS AND COMPLIANCE

Patients took the study drug on all seven days in 71.7 percent of cycles, and the percentages were similar in the two groups (Table 4). A failure of prophylaxis was defined by the onset of a febrile episode during prophylaxis, with documented compliance up to the day of infection. In the levofloxacin group, 25.8 percent of febrile episodes (25 of 97) were considered failures of prophylaxis, as compared with 40.4 percent of such episodes in the placebo group (61 of 151) (Table 4).

#### MICROBIOLOGIC OUTCOMES

The organism that was the probable cause of the febrile episode or episode of probable infection was isolated less frequently among patients in the levofloxacin group than among patients in the placebo group (7.2 percent vs. 14.6 percent and 4.6 percent vs. 12.6 percent, respectively) (Table 4). Gram-neg-

**Table 3. Incidence of Febrile Episodes, Probable Infections, and Hospitalization for Infection.\***

Event	Levofloxacin (N=781)	Placebo (N=784)	Relative Risk (95% CI)	P Value†
	<i>no. of patients (%)</i>			
<b>Events occurring in first cycle</b>				
Febrile episode				
Yes	27 (3.5)	62 (7.9)	0.44 (0.28–0.68)	<0.001
No	736	699		
Unknown	18	23		
Probable infection				
Yes	109 (14.0)	152 (19.4)	0.72 (0.57–0.90)	0.005
No	658	614		
Unknown	14	18		
Hospitalization for infection				
Yes	52 (6.7)	81 (10.3)	0.64 (0.46–0.90)	0.01
No	712	681		
Unknown	17	22		
<b>Events occurring at least once in any cycle</b>				
Febrile episode				
Yes for ≥1 cycles	84 (10.8)	119 (15.2)	0.71 (0.55–0.92)	0.01
No for all cycles	661	623		
Unknown for ≥1 cycles	36	42		
Probable infection				
Yes for ≥1 cycles	267 (34.2)	325 (41.5)	0.82 (0.73–0.94)	0.004
No for all cycles	489	432		
Unknown for ≥1 cycles	25	27		
Hospitalization for infection				
Yes for ≥1 cycles	123 (15.7)	169 (21.6)	0.73 (0.59–0.90)	0.004
No for all cycles	623	575		
Unknown for ≥1 cycles	35	40		
<b>Severe infection and/or death from infection</b>	8 (1.0)	16 (2.0)	0.50 (0.22–1.17)	0.15

\* A febrile episode was defined by a temperature of more than 38°C. CI denotes confidence interval.

† The P values, determined by the chi-square test, are for a “yes” answer as compared with a “no” answer or unknown status.

ative organisms were isolated on 37 occasions. Of the 13 isolates for which data on fluoroquinolone susceptibility were available, 12 were sensitive; the 1 resistant organism was from a patient in the placebo group (see Tables 1 and 2 of the Supplementary Appendix, available with the full text of this article at [www.nejm.org](http://www.nejm.org)). Of the eight probable instances of bacteremia in the levofloxacin group, three were regarded as the result of probable contaminants in the culture, two occurred outside the treatment period, and the other three occurred in patients who were not taking levofloxacin.

#### ADVERSE EVENTS

Adverse events were reported in 118 of 6869 cycles of chemotherapy (1.7 percent). There was a slight excess of adverse events in the levofloxacin group, owing to a higher rate of minor gastrointestinal symptoms and rash (Table 4).

#### DISCUSSION

We addressed the efficacy of antibacterial prophylaxis in patients treated for solid cancers with chemotherapy regimens associated with short periods

of neutropenia and thus an increased risk of infection. A simple, clinically relevant objective observation (fever, as defined by a temperature of more than 38°C) attributed to infection was chosen as the primary outcome measure because, in routine practice, this finding often triggers urgent treatment of infection in patients who may have neutropenia. Microbiologic confirmation was not required to meet this end point, since it was assumed that such a stipulation would result in the underreporting of infections and that prophylaxis might interfere with culture results, causing bias. Our results confirm this supposition: organisms were isolated in only a minority of febrile episodes (11.7 percent) and probable infections (9.2 percent), and organisms were isolated more frequently from cultures in the placebo group than in the levofloxacin group (Table 4). It is possible that some true episodes of infection were not reported and that some reported events attributed to bacterial infection were, in reality, due to other causes (e.g., viral infection). The occurrence of either possibility would tend to decrease the sensitivity of the trial to detect a true prophylactic effect of levofloxacin. However, the randomized, double-blind, placebo-controlled design means that any diagnostic inaccuracies were independent of treatment allocation and should not have biased the results.

To maximize the collection of data for the clinical end point in this large, multicenter trial of outpatients, we chose not to collect extensive data on the antibacterial resistance of infecting or colonizing isolates. This is an important limitation. Antibacterial prophylaxis might select for microbial resistance, and conversely, resistance patterns may affect prophylactic efficacy. Many factors affect the incidence of bacterial resistance, but there is a long history of misuse of antibacterial agents,<sup>12</sup> and a correlation between national levels of outpatient use of antibacterial agents and resistance has been demonstrated across Europe.<sup>13</sup> The effect on the development of resistance with the repeated use of short periods of fluoroquinolone prophylaxis on an outpatient basis among patients receiving cytotoxic chemotherapy is unknown. One possible consequence would be increasing bacterial resistance. Alternatively, a reduction in the incidence of hospitalization and the use of broad-spectrum antibacterial agents in that setting might reduce selection pressure for bacterial resistance among patients with cancer. This large, randomized controlled trial was designed to show whether levofloxacin prophylaxis

to reduce clinical infection is a rational approach in a defined group of at-risk patients. However, our results alone cannot be used to determine whether a policy of antibacterial prophylaxis should be applied systematically.

Thirteen percent of patients receiving conventional-dose chemotherapy for solid tumors or lymphoma had at least one febrile episode, with an overall incidence of 3.6 percent per cycle. During the entire course of chemotherapy, approximately one third fewer patients in the levofloxacin group than in the placebo group had a febrile episode (10.8 percent vs. 15.2 percent). The incidence of fever during the first cycle of chemotherapy among the patients in the levofloxacin group was less than half that among patients in the placebo group (3.5 percent vs. 7.9 percent). Not all infections are characterized by fever; hence, the inclusion of the outcome of probable infection. This category is heterogeneous, more dependent on the interpretation of clinical data by the physician, and more likely to include events that cannot be prevented by antibacterial prophylaxis. Thus, a smaller proportion of these events than of febrile episodes was associated with a neutrophil count of less than 100 per cubic millimeter. Levofloxacin prophylaxis was still associated with a significant reduction in the overall risk of probable infections. The overall incidence of severe infections was just 1.5 percent, and although the incidence was 50 percent lower with levofloxacin than with placebo, the trial was not powered statistically to detect the ability of prophylaxis to prevent severe infection or death from infection. The reduction in the incidence of hospitalization for the treatment of infection was significant and equivalent to a saving of about 38 hospital days per 100 patients given levofloxacin prophylaxis. Forty percent of fevers occurred outside the expected period of neutropenia (i.e., the period of prophylaxis) (Table 4). This finding calls into question the optimal timing and duration of prophylaxis. All severe infections and deaths from infection in the levofloxacin group occurred either outside the period of prophylaxis or among patients who were not taking the study drug. This finding emphasizes the importance of compliance.

A trial conducted by the European Organisation for Research and Treatment of Cancer<sup>14</sup> randomly assigned 163 patients with small-cell lung cancer to receive ciprofloxacin plus roxithromycin or placebo alone for 10 days after chemotherapy. The group that received prophylaxis had a marked reduction in infection-related outcomes, including death, partic-

**Table 4. Treatment Compliance, Adverse Events, and Characteristics of Febrile Episodes and Probable Infections.**

Variable	Levofloxacin	Placebo
<b>All cycles — no. (%)</b>	<b>3410</b>	<b>3459</b>
Compliance		
7 days of study drug	2470 (72.4)	2458 (71.1)
1–6 days of study drug	114 (3.3)	123 (3.6)
0 days of study drug	625 (18.3)	667 (19.3)
Unknown	201 (5.9)	211 (6.1)
Adverse event	78 (2.3)	40 (1.2)
Rash	22	13
Gastrointestinal effect	36	11
Central nervous system effect	6	6
Musculoskeletal effect	4	1
Multiple events, including those listed above	5	6
Other*	5	3
Unknown	31	27
Antifungal prophylaxis prescribed	271 (8.0)	266 (7.7)
Unknown	129	118
Incidence of mucosal candidiasis	159 (4.7)	176 (5.1)
Unknown	66	78
<b>Cycles with febrile episode — no. (%)</b>	<b>97 (100)</b>	<b>151 (100)</b>
Total — no. (%)		
During expected nadir in compliant patient	25 (25.8)	61 (40.4)
During expected nadir in noncompliant patient or one with unknown compliance status	29 (29.9)	19 (12.6)
Outside expected nadir	37 (38.1)	62 (41.1)
Unknown	6 (6.2)	9 (6.0)
Hospitalization — no. (%)	80 (82.5)	130 (86.1)
Duration — days†		
Median	6.5	5
Interquartile range	5–9	3–8
Total	608	813
Neutrophil count at onset of infection		
<1000/mm <sup>3</sup> — no. (%)	56 (57.7)	86 (57.0)
Unknown	13	13
Median — cells/mm <sup>3</sup>	300	520
Interquartile range — cells/mm <sup>3</sup>	100–1780	100–2500
Microbiologic analysis — no. (%)		
Probable causative bacteria isolated‡	7 (7.2)	22 (14.6)
Bacteremia	6 (6.2)	12 (7.9)
<b>Cycles with probable infection</b>		
Total — no. (%)	350 (100)	467 (100)
During expected nadir in compliant patient	85 (24.3)	166 (35.5)
During expected nadir in noncompliant patient or one with unknown compliance status	58 (16.6)	52 (11.1)
Outside expected nadir	169 (48.3)	210 (45.0)
Unknown	38 (10.9)	39 (8.4)

**Table 4. (Continued.)**

Variable	Levofloxacin	Placebo
Hospitalization for infection	145 (41.4)	209 (44.8)
Duration — days§		
Median	6	5
Interquartile range	4–9	4–8
Total	1101	1400
Neutrophil count at onset of infection		
<1000/mm <sup>3</sup> — no. (%)	109 (31.1)	151 (32.3)
Unknown	111	127
Median — cells / mm <sup>3</sup>	1200	1360
Interquartile range — cells/mm <sup>3</sup>	210–3700	380–4090
Microbiologic analysis — no (%)		
Probable causative bacteria isolated‡	16 (4.6)	59 (12.6)
Bacteremia	8 (2.3)	18 (3.8)

\* This category includes allergic reactions, a general feeling of malaise, breathlessness, chest discomfort, and unspecified events.

† The analysis was confined to patients whose infections led to hospitalization. The duration of hospitalization was unknown for four patients in the placebo group and two in the levofloxacin group.

‡ This category includes bacteremias.

§ The analysis was confined to patients whose infections led to hospitalization. The duration of hospitalization was unknown for nine patients in the placebo group and five in the levofloxacin group.

ularly in a cohort receiving intensified chemotherapy with G-CSF. We extend these findings, reporting a significant benefit from single-agent prophylaxis for seven days in a much larger cohort of patients with a wide spectrum of cancers and treatments, including 220 patients who received nonintensified chemotherapy for small-cell lung cancer with no G-CSF.

There is more than one strategy for using the limited repertoire of orally bioavailable antibacterial agents to combat neutropenic infection. Instead of routine prophylaxis, fluoroquinolones might be used empirically to treat neutropenic infections in patients predicted to be at low risk for complications.<sup>15</sup> To date, trials comparing fluoroquinolones with intravenous antibiotics have required patients to be hospitalized until fever and neutropenia resolve,<sup>16,17</sup> so routine use of this alternative approach is not yet appropriate for patients receiving chemotherapy.

In conclusion, the administration of levofloxacin for seven days to cover the expected period of severe neutropenia after cyclic, standard-dose, myelosuppressive chemotherapy in patients with solid cancers or lymphoma significantly reduced the incidence of clinically documented infection and hospitalization for the treatment of neutropenic infection, with minimal adverse effects. The small

number of isolates identified and the incomplete susceptibility data did not allow us to determine the effect of prophylaxis on antibacterial resistance.

Our findings can be used to develop rational strategies to minimize the effect of infection during neutropenia in patients with cancer. Our results complement the positive findings of a contemporaneous Italian collaborative trial of levofloxacin prophylaxis reported elsewhere in this issue of the *Journal*.<sup>18</sup> Taken together, the findings call for detailed microbiologic studies to determine whether the demonstrated clinical benefit is associated with resistance problems in the wider community of patients with cancer.

Hoechst Marion Roussel (now part of Sanofi Aventis) provided an educational grant and trial medication. Cancer Research UK provides a core grant to the Clinical Trials Unit, Birmingham.

Dr. Cullen reports having received research grant support from Eli Lilly and Sanofi Aventis and having received lecture fees from and having served on paid advisory boards for Sanofi Aventis, Eli Lilly, and AstraZeneca. Dr. Rea reports having received research grant support from Sanofi Aventis and having received lecture fees from Pfizer. Mr. Stanley reports having received lecture fees from Sanofi Aventis, Bristol-Myers Squibb, and AstraZeneca. Dr. Gollins reports having received research grant support from Sanofi Aventis and Roche.

We are indebted to Drs. Christopher Gallagher, Gordon Rustin, and Jim Slattery and Prof. Michael Whitehouse (data monitoring and ethics committee); to Susan Whitmarsh (pharmacy); and to Sarah Bathers, Rebecca Hindle, Helen Howard, Mary Ann Macham, Julia Mason, Caroline Price, and Steve Harris (trial coordination and information-technology support) for their help and support.

## APPENDIX

In addition to the authors, the following investigators participated in the SIGNIFICANT Trial: S. Al-Ismail (Singleton, Swansea), A. Al-Samarraie (Glan Clwyd, Rhyl), C. Alcock (Stoke Mandeville, Aylesbury), R. Allerton (New Cross, Wolverhampton), A. Anthony (Cookridge, Leeds), A. Axford (Bronlais General, Aberystwyth), N. Bailey (Derriford, Plymouth and Torbay), J. Barber (Velindre, Cardiff), D. Bareford (City Hospital, Birmingham), A. Barrett (Western Infirmary, Glasgow), P. Barrett-Lee (Velindre, Cardiff), N. Bates (Stoke Mandeville, Aylesbury), E. Bessell (Nottingham City), J. Bishop (Glan Clwyd, Rhyl, and Ysbyty Gwynedd, Bangor), A. Biswas (Royal Preston), P. Bliss (Royal Devon and Exeter and Torbay), S. Bolam (Taunton and Somerset), M. Bond (Cookridge, Leeds), C. Brammer (Kidderminster and New Cross, Wolverhampton), A. Brewster (Royal Gwent and Velindre), A. Brownell (Oldchurch, Romford), J. Carmichael (Nottingham City), P. Chakraborti (Derbyshire Royal Infirmary, Derby), A. Champion (Glan Clwyd, Rhyl), A. Chetiyawardana (Queen Elizabeth, Birmingham), M. Churn (Kidderminster and New Cross, Wolverhampton), P. Clark (Clatterbridge, Wirral), J. Clarke (Belvoir Park, Belfast), M. Collinson (Royal Cornwall, Truro), S. Crawford (Airedale, Keighley), D. Dearnley (Royal Marsden, London), D. Dodwell (Cookridge, Leeds), D. Dunlop (Western Infirmary, Glasgow), D. Edwards (Glan Clwyd, Rhyl), S. Elyan (Cheltenham General, Cheltenham), D. Farrugia (Cheltenham General, Cheltenham), D. Fermont (Northwick Park, Harrow), D. Fyfe (Nottingham City), C. Gaffney (Royal Gwent, Newport and Velindre, Cardiff), J. Gardiner (North Tyneside General, North Shields), D. Gilligan (Hinchingsbrooke, Huntingdon), A. Goodman (Royal Devon and Exeter and Torbay), D. Gozzard (Glan Clwyd, Rhyl), T. Gulliford (St. Mary's, Portsmouth), D. Guthrie (Derbyshire Royal Infirmary, Derby), B. Hancock (Weston Park, Sheffield), P. Harper (Guy's and St. Thomas', London), P. Harrison (Russell's Hall, Dudley), Y. Hassan (Sandwell General, West Bromwich), A. Hong (Royal Devon and Exeter and Torbay), A. Horwich (Royal Marsden, Sutton), S. Houston (Royal Surrey County, Guildford), T. Iveson (Royal South Hants, Southampton), P. Jenkins (Cheltenham General, Cheltenham), J. Joffe (Huddersfield Royal Infirmary, Huddersfield), P. Johnson (Royal South Hants, Southampton), S. Kaye (Western Infirmary, Glasgow), S. Kumar (Pinderfields General, Wakefield), S. Lewis (Singleton, Swansea), F. MacBeth (Llandough, Cardiff), P. Mack (Diana Princess of Wales, Grimsby), E. Marshall (Clatterbridge, Wirral), T. Maughan (Velindre Hospital, Cardiff), K. McAdam (Addenbrookes, Cambridge and Peterborough), J. McAleer (Belfast City Hospital, Belfast), G. Mead (Royal South Hants, Southampton), R. Mehra (New Cross, Wolverhampton), S. Morgan (Nottingham City), M. Muers (Leeds General Infirmary, Leeds), J. Murray (Queen Elizabeth, Birmingham), P. Murray (Essex County, Colchester), A. Neal (Essex County, Colchester), J. Neilson (Russell's Hall, Dudley), A. Nethersell (Glan Clwyd, Rhyl), M. O'Brien (Royal Marsden, Sutton and Kent Oncology Centre, Maidstone), A. O'Callaghan (St. Mary's, Portsmouth), S. O'Reilly (Clatterbridge, Wirral), C. Ottensmeier (Royal South Hants, Southampton), J. Owen (Cheltenham General, Cheltenham), D. Peake (City Hospital and Queen Elizabeth, Birmingham), I. Pedley (Newcastle General, Newcastle), C. Poole (City Hospital and Queen Elizabeth, Birmingham), D. Prangnell (Lincoln County), B. Pratt (Essex County, Colchester), M. Quigley (Oldchurch, Romford), A. Rathmell (James Cook, Middlesbrough), F. Roberts (Pontefract), S. Sadullah (James Paget, Great Yarmouth), A. Samanci (Glan Clwyd, Rhyl), J. Seale (Ysbyty Gwynedd, Bangor), D. Sebag-Montefiore (Pinderfields, Wakefield), J. Shamash (Oldchurch, Romford), H. Smedley (Kent Oncology Centre, Canterbury), D. Smith (Clatterbridge, Wirral), I. Smith (Royal Marsden, London and Sutton), S. Smith (Torbay), M. Snee (Cookridge, Leeds), M. Sokal (Nottingham City), T. Sreenivasan (Scunthorpe General), P. Stableforth (Sandwell General, West Bromwich), N. Storey (James Cook University, Middlesbrough), C. Tiplady (North Tyneside General, North Shields), D. Turner (Torbay), S. Upadhyay (Diana Princess of Wales, Grimsby), P. Vasey (Western Infirmary, Glasgow), N. Wadd (James Cook University, Middlesbrough), D. Wheatley (Royal Cornwall, Truro), M. Williams (Addenbrookes, Cambridge and Hinchingsbrooke, Huntingdon), P. Woll (Nottingham City), J. Wright (City Hospital, Birmingham), H. Yosef (Hairmyres, East Kilbride).

## REFERENCES

1. Tjan-Heijnen VC, Caleo S, Postmus PE, et al. Economic evaluation of antibiotic prophylaxis in small-cell lung cancer patients receiving chemotherapy: an EORTC double-blind placebo-controlled phase III study (08923). *Ann Oncol* 2003;14:248-57.
2. Leonard RC, Miles D, Thomas R, Nussey F. Impact of neutropenia on delivering planned adjuvant chemotherapy: UK audit of primary breast cancer patients. *Br J Cancer* 2003;89:2062-8.
3. Sullivan KM, Dykewicz CA, Longworth DL, et al. Preventing opportunistic infections after hematopoietic stem cell transplantation: the Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation Practice Guidelines and Beyond. *Hematology (Am Soc Hematol Educ Program)* 2001:392-421.
4. Ozer H, Armitage JO, Bennett CL, et al. 2000 Update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol* 2000;18:3558-85.
5. Hughes WT, Armstrong D, Bodey GP, et al. 1997 Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis* 1997;25:551-73.
6. Freifeld A, McNabb J, Anderson J, Ulrich FA. Low-risk patients with fever and neutropenia during chemotherapy: current clinical practice patterns. *Proc Am Soc Clin Oncol* 2004;23:747. abstract.
7. Verhoef J. Prevention of infections in the neutropenic patient. *Clin Infect Dis* 1993;17:Suppl 2:S359-S367.
8. Spiers AS, Tattersall MH, Gaya H. Indications for systemic antibiotic prophylaxis in neutropenic patients. *Br Med J* 1974;4:440-1.
9. Engels EA, Lau J, Barza M. Efficacy of quinolone prophylaxis in neutropenic cancer patients: a meta-analysis. *J Clin Oncol* 1998;16:1179-87.
10. Cruciani M, Rampazzo R, Malena M, et al. Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis* 1996;23:795-805.
11. Fu KP, Lafredo SC, Foleo B, et al. In vitro and in vivo antibacterial activities of levofloxacin (l-ofloxacin), an optically active ofloxacin. *Antimicrob Agents Chemother* 1992;36:860-6.
12. Levy SB, Marshall B. Antibacterial resistance worldwide: causes, challenges and responses. *Nat Med* 2004;10:Suppl 12:S122-S129.
13. Goossens H, Ferech M, Vander Stichele R, Elseviers M. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.
14. Tjan-Heijnen VC, Postmus PE, Ardizzone A, et al. Reduction of chemotherapy-induced febrile leucopenia by prophylactic use of ciprofloxacin and roxithromycin in small-cell lung cancer patients: an EORTC double-blind placebo-controlled phase III study. *Ann Oncol* 2001;12:1359-68.
15. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000;18:3038-51.
16. Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med* 1999;341:305-11.
17. Kern WV, Cometta A, De Bock R, Lange-naeken J, Paesmans M, Gaya H. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. *N Engl J Med* 1999;341:312-8.
18. Bucaneve G, Micozzi A, Menichetti F, et al. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med* 2005;353:977-87.

Copyright © 2005 Massachusetts Medical Society.