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A DOUBLE-BLIND COMPARISON OF EMPIRICAL ORAL AND INTRAVENOUS ANTIBIOTIC THERAPY FOR LOW-RISK FEBRILE PATIENTS WITH NEUTROPENIA DURING CANCER CHEMOTHERAPY

ALISON FREIFELD, M.D., DONNA MARCHIGIANI, R.N., THOMAS WALSH, M.D., STEPHEN CHANOCK, M.D., LINDA LEWIS, M.D.,
JOHN HIEMENZ, M.D., SHARON HIEMENZ, R.N., JEANNE E. HICKS, M.D., VEE GILL, PH.D., SETH M. STEINBERG, PH.D.,
AND PHILIP A. PIZZO, M.D.

ABSTRACT

Background Among patients with fever and neutropenia during cancer chemotherapy who have a low risk of complications, oral administration of empirical broad-spectrum antibiotics may be an acceptable alternative to intravenous treatment.

Methods We conducted a randomized, double-blind, placebo-controlled study of patients (age, 5 to 74 years) who had fever and neutropenia during chemotherapy for cancer. Neutropenia was expected to be present for no more than 10 days in these patients, and they had to have no other underlying conditions. Patients were assigned to receive either oral ciprofloxacin plus amoxicillin-clavulanate or intravenous ceftazidime. They were hospitalized until fever and neutropenia resolved.

Results A total of 116 episodes were included in each group (84 patients in the oral-therapy group and 79 patients in the intravenous-therapy group). The mean neutrophil counts at admission were 81 per cubic millimeter and 84 per cubic millimeter, respectively; the mean duration of neutropenia was 3.4 and 3.8 days, respectively. Treatment was successful without the need for modifications in 71 percent of episodes in the oral-therapy group and 67 percent of episodes in the intravenous-therapy group (difference between groups, 3 percent; 95 percent confidence interval, -8 percent to 15 percent; $P=0.48$). Treatment was considered to have failed because of the need for modifications in the regimen in 13 percent and 32 percent of episodes, respectively ($P<0.001$) and because of the patient's inability to tolerate the regimen in 16 percent and 1 percent of episodes, respectively ($P<0.001$). There were no deaths. The incidence of intolerance of the oral antibiotics was 16 percent, as compared with 8 percent for placebo ($P=0.07$).

Conclusions In hospitalized low-risk patients who have fever and neutropenia during cancer chemotherapy, empirical therapy with oral ciprofloxacin and amoxicillin-clavulanate is safe and effective. (N Engl J Med 1999;341:305-11.)

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DURING the treatment of cancer, the appearance of fever with neutropenia is the first manifestation of a potentially life-threatening bacterial infection.¹ Prompt hospitalization of patients with cancer who have fever and neutropenia and initiation of empirical intravenous therapy with broad-spectrum antibiotics are the standard of care. In over half of patients so treated, however, no infectious source is found.²

Studies suggest that patients with cancer who have fever and neutropenia can be stratified into low-risk and high-risk groups, primarily according to the expected duration of neutropenia and the presence or absence of other underlying conditions (e.g., hypotension, pulmonary compromise, and abdominal pain).³⁻⁶ Low-risk patients with fever who have had neutropenia for no more than 7 to 10 days and who do not have any other underlying conditions have fewer medical complications and a lower risk of death than high-risk patients.⁶⁻⁹ Therefore, inpatient treatment with intravenous antibiotics may be unnecessary for low-risk patients, and a simplified empirical regimen of broad-spectrum oral antibiotics may be adequate.⁷⁻⁹

We conducted a randomized, double-blind, placebo-controlled comparison of standard intravenous monotherapy with ceftazidime and an oral regimen of ciprofloxacin plus amoxicillin-clavulanate as initial treatment in febrile patients with neutropenia who were at low risk for complications. The combination of ciprofloxacin and amoxicillin-clavulanate provides coverage similar to that of ceftazidime, in-

From the National Cancer Institute (A.F., D.M., T.W., S.C., L.L., S.M.S.) and the Warren Grant Magnusen Clinical Center (J.E.H., V.G.), National Institutes of Health, Bethesda, Md.; the H. Lee Moffitt Cancer Center, University of South Florida, Tampa (J.H., S.H.); and Children's Hospital and Harvard Medical School, Boston (P.A.P.). Address reprint requests to Dr. Freifeld at the University of Nebraska Medical Center, Infectious Diseases Section, 985400 Nebraska Medical Center, Omaha, NE 68198-5400.

cluding potent activity against *Pseudomonas aeruginosa* and most other common pathogens associated with fever in patients with neutropenia. The goal of this study was to determine whether a broad-spectrum oral regimen was an acceptable alternative to a regimen of parenteral antibiotics in hospitalized low-risk patients.

METHODS

From May 1992 through July 1997 patients with cancer who were at least five years of age and who had fever with neutropenia were eligible if their neutropenia was expected to resolve within 10 days after the onset of fever and if they did not have hemodynamic instability, abdominal pain, nausea and vomiting, diarrhea (passage of six loose stools daily), neurologic or mental-status changes, intravascular-catheter infection, catheter-tunnel infection, or a new pulmonary infiltrate. These criteria were considered to indicate a low risk of infectious complications. Patients also had to be able to swallow orally administered study medications without vomiting and to have adequate hepatic function (defined as aminotransferase values that were less than five times the normal values) and renal function (defined as a creatinine clearance of at least 30 ml per minute). Patients with allergies to any study agent and those who had received antibiotics within 72 hours before the study began were ineligible. Prophylactic use of acyclovir and trimethoprim-sulfamethoxazole was permitted. All patients or their parents or guardians provided written informed consent.

Patients were excluded if their neutropenia was expected to last for more than 10 days after the onset of infection or if they had a serious coexisting medical condition, since these factors were considered to indicate a high risk of complications. Patients who had undergone autologous stem-cell transplantation, those with human immunodeficiency virus infection, and those who were pregnant were also excluded. Treatment with calcium- or magnesium-containing oral agents, theophylline, probenecid, or allopurinol was not permitted during the study. Patients were permitted to receive growth factors and cytokines.

Fever was considered to be present if the temperature was 38°C or higher on three oral measurements obtained 4 hours apart during a 24-hour period or if the oral temperature was 38.5°C or higher on a single measurement. Neutropenia was defined as an absolute neutrophil count of less than 500 polymorphonuclear leukocytes per cubic millimeter. Febrile patients whose absolute neutrophil counts were expected to drop below 500 per cubic millimeter within 24 hours after entry into the study were eligible.

Study Design

A history was obtained and a physical examination was performed on each patient within an hour after presentation. A complete blood count, blood chemical and coagulation tests, chest radiography, urinalysis, and cultures of blood and urine were performed before empirical therapy was begun. At least one specimen of blood for aerobic and anaerobic cultures was drawn through a catheter lumen (if present) and another from a peripheral vein. In patients with positive blood and urine cultures, cultures were repeated after 48 hours of empirical therapy.

After the initial evaluation, patients were randomly assigned to receive either the oral regimen consisting of 30 mg of ciprofloxacin per kilogram of body weight per day in three divided doses (maximal dose, 750 mg every eight hours) (Cipro, Bayer, West Haven, Conn.) plus 40 mg of amoxicillin-clavulanate per kilogram per day in three divided doses (maximal dose, 500 mg every eight hours) (Augmentin, SmithKline Beecham Pharmaceuticals, Philadelphia) or the intravenous regimen consisting of 90 mg of ceftazidime per kilogram per day in three divided doses (maximal dose, 2 g every eight hours) (Fortaz, Glaxo, Research Triangle Park, N.C.). Each active regimen was paired with a placebo preparation, so that both an oral and an intravenous study agent were

given every eight hours. Patients who could not easily swallow tablets because they had mild mucositis or were very young were given an equivalent dose of oral amoxicillin-clavulanate or its placebo in liquid form. Oral placebo formulations matching those of ciprofloxacin and amoxicillin-clavulanate were supplied by the pharmaceutical companies that provided the active drugs. The intravenous placebo solution consisted of 5 percent dextrose plus multivitamins.

Patients continued treatment until the resolution of neutropenia, which was defined as an increase in the neutrophil count to 500 per cubic millimeter or greater. With recovery of the count to 500 per cubic millimeter, patients with no documented cause of infection could be discharged if they were afebrile. Those with documented infections could be switched to appropriate open-label antibiotics. All patients were hospitalized until the fever and neutropenia resolved.

Clinical Assessments and Changes in Treatment Regimens

The patients were assessed and complete blood counts were performed daily until the neutropenia resolved, and blood chemical and coagulation values were obtained every third day. Blood was drawn daily for cultures from patients with persistent fever. Chest radiographs were obtained and invasive procedures performed as clinically indicated. Classification of the initial episode of fever as either unexplained or the result of a clinically or microbiologically defined infection was based on data gathered within the first 72 hours after entry into the study, as described previously.^{10,11}

Changes in treatment regimens were made according to predefined criteria and were based on the results of the physical examination, microbiologic cultures, and radiography. Any modifications took into account the antimicrobial spectrum of the study drugs, since the investigators were unaware of the antibiotics that each patient actually received. Antimicrobial agents were added if the patient had clinical or microbiologic evidence of an infection that was presumed or known to be inadequately treated by either study regimen. Vancomycin was added if coagulase-negative staphylococcus was obtained from two pretreatment cultures of blood drawn through the intravascular catheter or if gram-positive isolates were obtained from one pretreatment culture. If a gram-negative organism was isolated from cultures of blood drawn through the intravascular catheter, the patient was switched to an appropriate open-label regimen of intravenous antibiotics.

Persistent fever was not a criterion for a change in the treatment regimen, with one exception: empirical antifungal therapy was added when fever persisted or recrudesced after five days of antibiotics. An antifungal agent or acyclovir was added if there was clinical or microbiologic evidence of invasive fungal or herpes simplex virus infection, respectively.

Study medications were discontinued and treatment was switched to open-label ceftazidime if the patients could not tolerate oral medications because of mucositis, diarrhea, nausea and vomiting, or rash. When hemodynamic instability, progressive primary infection, or breakthrough infection (an infection that was not present on initial evaluation but that was detected after 72 hours of study treatment) developed, the treatment was changed to the backup regimen of imipenem plus gentamicin or to specific antibiotics, depending on the results of microbiologic assessments.

Evaluation of Responses and Adverse Effects

Clinical outcomes were prospectively defined. Empirical therapy was considered to have been successful if the patient survived the episode of fever and neutropenia without any modifications in the assigned regimen, and without evidence of active infection at the time of the resolution of neutropenia. Treatment was considered to have failed if the regimen had to be modified by the addition of one or more antibacterial, antiviral, or antifungal agents or if treatment was changed to the backup regimen for progressive or breakthrough infection, or if treatment was switched to open-label intravenous antibiotics because of severe mucositis, nausea and vomiting, rash, or diarrhea. However, treatment was

not considered to have failed in patients assigned to intravenous ceftazidime who could not tolerate oral placebo, since these patients continued to receive open-label ceftazidime. These patients were identified after the study assignments were revealed.

Hepatotoxicity, nephrotoxicity, and hematologic toxicity were defined according to the Common Toxicity Criteria of the National Cancer Institute.¹² Diarrhea (six loose stools per day) or nausea and vomiting that began after the initiation of empirical therapy were considered adverse effects. The protocol specified that all patients who were 18 years of age or younger should undergo gait and joint assessments by a rheumatologist approximately every 72 hours during the study.^{13,14}

Statistical Analysis

A total of 115 episodes of fever and neutropenia were required in each group for the study to have the power to determine whether the two regimens were equivalent in terms of efficacy with an α level of 0.20 and a β error of 0.05, and with the rate of success of standard intravenous therapy assumed to be 70 percent. The regimens were considered equivalent if the absolute difference in the proportion of successful outcomes between groups did not exceed 15 percent.¹⁵

We used the chi-square test or Fisher's exact test to compare various outcomes between groups. We used the Wilcoxon rank-sum test to compare continuous variables and the Mantel-Haenszel test to compare differences in the duration of fever between the groups. We also assessed the statistical independence of data obtained from patients who were enrolled more than once.

RESULTS

Characteristics of the Patients

From May 1992 until July 1997, 211 patients had a total of 284 episodes of fever and neutropenia. Fifty-two episodes were not evaluated and were evenly distributed in the two groups. Thirty of these 52 episodes were excluded because of protocol violations (the addition of antibiotics without the approval of study investigators or the concomitant use of prohibited oral medications), 18 because it was discovered after randomization that eligibility criteria had not been met, and 4 because patients declined to continue the study. Among the 232 remaining episodes (in 163 patients), 208 occurred in patients who were enrolled at the National Cancer Institute and 24 occurred in patients enrolled at the H. Lee Moffitt Cancer Center. Among the 232 patients, 46 were enrolled more than once: 28 had two episodes, 13 had three episodes, and 5 had four episodes.

There were 116 episodes in each group (Table 1). There were 84 patients in the group assigned to receive oral ciprofloxacin and amoxicillin-clavulanate, and 79 patients in the group assigned to receive intravenous ceftazidime. The two groups were similar with respect to age, sex, and type of cancer. Most of the patients were women with breast cancer. In 80 of the episodes among patients given oral therapy and 90 of the episodes among patients given intravenous therapy, the affected patients had a central intravascular catheter. During 37 episodes a granulocyte-macrophage colony-stimulating factor was given in addition to the assigned treatment; a granulocyte colony-stimulating factor was administered

TABLE 1. CHARACTERISTICS OF THE PATIENTS WITH EPISODES OF FEVER AND NEUTROPENIA.*

CHARACTERISTIC	ORAL CIPROFLOXACIN AND AMOXICILLIN-CLAVULANATE (N=116)	INTRAVENOUS CEFTAZIDIME (N=116)
Age — yr		
Mean	42	41
Range	5-74	8-69
Sex — no. (%)		
Female	90 (78)	89 (77)
Male	26 (22)	27 (23)
Type of cancer — no. (%)		
Leukemia or lymphoma	29 (25)	34 (29)
Solid tumor	87 (75)	82 (71)
Neutropenia		
Mean neutrophil count on admission — cells/mm ³	81	84
Neutrophil count <100/mm ³ on admission — no. (%)	91 (78)	87 (75)
Duration of neutropenia — days		
Mean	3.4	3.8
Range	1-8	1-14
Cause of fever — no. (%)		
Unexplained	79 (68)	70 (60)
Documented infection†	37 (32)	46 (40)
Bloodstream	5‡	12§
Subcutaneous tissue (cellulitis)	8	4
Upper respiratory tract	3	3
Oropharynx	19	24
Gastrointestinal tract	2	9
Urinary tract	8	5

*The numbers refer to the numbers of episodes.

†Documented infections were clinically or microbiologically documented. Some episodes involved multiple documented infections.

‡Four of these infections were related to the catheter.

§Five of these infections were related to the catheter.

during 163 episodes; an interleukin was given during 4 episodes; and no growth factors or cytokines were given during 28 episodes. With the exception of interleukin therapy (given in all four cases to patients in the intravenous-therapy group), these treatments were distributed evenly between the two groups. In at least 75 percent of the episodes in both groups, the patients had an initial neutrophil count of less than 100 per cubic millimeter. The mean duration of neutropenia was approximately 3.4 days in the oral-therapy group and 3.8 days in the intravenous-therapy group.

Evaluation before Antibiotic Therapy

The cause of approximately two thirds of all febrile episodes was unexplained (Table 1). Infection was documented in 32 percent of the episodes in the oral-therapy group and 40 percent of the episodes in the intravenous-therapy group. Most documented infections were localized and were mild or moderate. The most common documented infections were severe oral or esophageal mucositis, which developed soon after randomization, prevented swallowing, and was

associated with persistent fever (11 episodes) and oropharyngeal reactivations of herpes simplex virus infections (23 episodes). Other types of infections included cellulitis at sites of indwelling central venous catheters or in the limbs or perianal region (eight episodes in the oral-therapy group and four episodes in the intravenous-therapy group), urinary tract infections (eight and five episodes, respectively), sinusitis (three and four episodes, respectively), viral upper respiratory tract infections (three episodes in each group), genital herpes (three episodes in each group), *Clostridium difficile* enteritis (one and six episodes, respectively), and cecitis (one episode in each group).

Cultures of blood obtained before the initiation of empirical therapy were positive in 17 episodes (7 percent) (Table 2). Coagulase-negative staphylococci (five episodes) and *Escherichia coli* (four episodes) were the predominant bloodstream isolates.

Efficacy of Oral and Intravenous Therapy

In the initial analysis performed before the treatment assignments were revealed, the efficacy of the oral and intravenous regimens was similar (71 percent vs. 59 percent; difference between groups, 11.2 percent; 95 percent confidence interval, -1 percent to 24 percent; $P=0.07$). After the assignments were revealed, the data were adjusted to reflect the fact that ceftazidime therapy was considered successful even if there was intolerance of oral placebo, since treatment in these patients was "switched" to open-label intravenous ceftazidime. In other words, in nine episodes in which treatment was considered before unblind-

ing to have failed, after unblinding treatment was revealed to have succeeded. Analysis of the adjusted data indicated that treatment was successful in 71 percent of the episodes in the oral-therapy group and 67 percent of the episodes in the intravenous-therapy group (difference between groups, 3 percent; 95 percent confidence interval, -8 percent to 15 percent; $P=0.48$) (Table 3). Tests of the statistical independence of data obtained from patients who were enrolled more than once confirmed that the outcome of the first episode had no effect on the outcome of the second episode if the same regimen was used (data not shown).

Although the failure rates were similar in the two groups, failure was more likely to have resulted from the need to add antimicrobial agents in the intravenous-therapy group than in the oral-therapy group (32 percent vs. 13 percent, $P<0.001$). Intolerance of active study drug resulted in failure in 16 percent of the episodes that were treated with oral antibiotics as compared with 1 percent of the episodes that were treated with intravenous antibiotics ($P<0.001$). Nausea and vomiting, mucositis, or rash led to the discontinuation of the oral regimen, whereas a single episode of rash during infusion led to the discontinuation of intravenous ceftazidime.

There was a trend toward a higher incidence of intolerance of the active oral antibiotics than of the oral placebo (16 percent vs. 8 percent, $P=0.07$) (Table 3). Mucositis was not a common reason for the discontinuation of oral medications. Of the 44 episodes of fever and neutropenia among patients who had mild mucositis at enrollment, 9 episodes (5 in the oral-therapy group and 4 in the intravenous-therapy group) eventually involved a switch to open-label intravenous therapy. Mucositis developed during four episodes in patients who were asymptomatic on entry (two in each group) and required a switch to open-label intravenous ceftazidime.

In approximately half the episodes in both groups, the fever had disappeared by day 2 of treatment ($P=0.65$). By day 5, fever had resolved in 90 percent of all episodes. Clinically significant hypotension occurred during three episodes, all of which occurred in patients in the intravenous-therapy group, and in each case it resolved when treatment was switched to the backup regimen. Bacteremia with cecitis or intraabdominal abscess was the cause of hypotension in two episodes; the other instance of hypotension occurred during a culture-negative episode of fever and neutropenia.

Outcome of Fever of Unexplained Origin

Fever of unexplained origin was successfully treated in 85 percent of the episodes in the oral-therapy group (67 of 79) and 90 percent of the episodes in the intravenous-therapy group (63 of 70). Treatment was considered to have failed because of a need for

TABLE 2. BLOODSTREAM ISOLATES OBTAINED BEFORE THE INITIATION OF EMPIRICAL THERAPY.

ORGANISM	ORAL CIPROFLOXACIN AND AMOXICILLIN- CLAVULANATE	INTRAVENOUS CEFTAZIDIME
	no. of episodes	
Gram positive		
Coagulase-negative staphylococcus	3	2
Streptococcus	0	1
<i>Clostridium septicum</i>	0	1
<i>Enterococcus faecalis</i>	0	1
Corynebacterium	0	1*
Gram negative		
<i>Escherichia coli</i>	1	3
Enterobacter	0	1
Klebsiella	1	1
Moraxella	0	1
Acinetobacter	0	1
Total†	5	13

*The isolate was not *Corynebacterium jeikeium*.

†Blood cultures were positive in a total of 17 episodes, since there was one multiorganism bloodstream infection (involving coagulase-negative staphylococcus and acinetobacter) in the intravenous-therapy group.

TABLE 3. ADJUSTED OUTCOMES OF EMPIRICAL THERAPY FOR EPISODES OF FEVER AND NEUTROPENIA IN LOW-RISK PATIENTS WITH CANCER.

OUTCOME	ORAL CIPROFLOXACIN AND AMOXICILLIN-CLAVULANATE (N=116)	INTRAVENOUS CEFTAZIDIME (N=116)	DIFFERENCE BETWEEN GROUPS (95% CI)*
	no. of episodes (%)		percent
Success	82 (71)	78 (67)†	3 (-8 to 15)
Failure	34 (29)	38 (33)	
Modification required‡	15 (13)	37 (32)	-19 (-29 to -9)
Addition of antibiotic	8	21	
Addition of antifungal agent	1	8	
Addition of antiviral agent	9	10	
Switch to open-label ceftazidime for catheter-related infection	1	—	
Switch to backup regimen	2	6	
Intolerance of oral study drug	19 (16)	9 (8)†	9 (0 to 17)
Intolerance of intravenous study drug	0	1 (1)	

*Values have been rounded. CI denotes confidence interval.

†Data were adjusted after treatment assignments were revealed and thus include the nine episodes in which patients received intravenous ceftazidime but could not tolerate oral placebo and thus were “switched” to open-label intravenous ceftazidime. Since these patients were already receiving intravenous ceftazidime, treatment was not considered truly to have failed.

‡Some episodes required more than one modification.

TABLE 4. OUTCOMES OF EMPIRICAL THERAPY FOR EPISODES OF FEVER AND NEUTROPENIA IN LOW-RISK PATIENTS WITH DOCUMENTED INFECTIONS.

OUTCOME	ORAL CIPROFLOXACIN AND AMOXICILLIN-CLAVULANATE (N=37)	INTRAVENOUS CEFTAZIDIME (N=46)	DIFFERENCE BETWEEN GROUPS (95% CI)*
	no. of episodes (%)		percent
Success	15 (41)	15 (33)	8 (-13 to 29)
Failure	22 (59)	31 (67)	
Modification required†	14 (38)	31 (67)	-30 (-50 to -9)
Addition of antibiotic	8	20	
Addition of antifungal agent	0	6	
Addition of antiviral agent	9	10	
Switch to open-label ceftazidime for catheter-related infection	1	—	
Switch to backup regimen	1	3	
Intolerance of active study drug	8 (22)	0	22 (8 to 35)

*Values have been rounded. CI denotes confidence interval.

†Some episodes required more than one modification.

a change in the regimen in 1 percent of the episodes in the oral-therapy group and 9 percent of the episodes in the intravenous-therapy group (P=0.15). One episode required the addition of vancomycin, three required the addition of an antifungal agent, and four required a switch to the backup regimen.

Outcomes of Documented Infections

Treatment was successful in 41 percent of the episodes of documented infection in the oral-therapy

group (15 of 37) and 33 percent of those in the intravenous-therapy group (15 of 46; difference between groups, 8 percent; 95 percent confidence interval, -13 percent to 29 percent; P=0.4) (Table 4). Treatment failed in approximately two thirds of episodes of documented infection. Failure resulted from the need to change the regimen in 38 percent of the episodes in the oral-therapy group and 67 percent of the episodes in the intravenous-therapy group (P=0.005). Intolerance of the active study

drug was the reason for treatment failure in 22 percent of episodes in the oral-therapy group but in none of the episodes in the intravenous-therapy group.

The majority of changes in the regimens in both groups consisted of the addition of vancomycin or antianaerobic agents or the addition of acyclovir for reactivations of oral herpes simplex virus infections (Table 4). Four of the 10 documented gram-negative bloodstream infections were managed without changing the regimen, including two cases of *E. coli* bacteremia that were successfully treated with oral antibiotics alone.

Breakthrough Infections

There were five breakthrough infections in the oral-therapy group and six in the intravenous-therapy group. A β -lactam-resistant strain of *E. coli* caused a breakthrough bloodstream infection in the intravenous-therapy group. Other breakthrough infections resulted in cellulitis, mucositis, or dental infections and were readily controlled by appropriate modifications in the antibiotic regimen.

Adverse Effects

Adverse effects occurred in 29 percent of episodes in the oral-therapy group and required early withdrawal from the study in 9 percent, primarily because of nausea and vomiting (Table 5). Treatment was not discontinued in most episodes in the oral-therapy group in which diarrhea was an adverse effect (22 of 23). Adverse effects occurred in 7 percent of episodes in the intravenous-therapy group but led to withdrawal from the study in only one episode (1 percent).

Thirteen of the 20 episodes among the children who were enrolled (mean age, 12.8 years; range, 5 to

18) were evaluated for joint-related adverse effects (7 in the oral-therapy group and 6 in the intravenous-therapy group). Transient shoulder pain occurred during two episodes in the intravenous-therapy group but in no episodes in the oral-therapy group.

DISCUSSION

We found that the combination of oral ciprofloxacin and amoxicillin-clavulanate was as effective as intravenous ceftazidime alone for the empirical management of fever during chemotherapy-induced neutropenia in hospitalized low-risk patients. Treatment was successful in nearly 70 percent of all episodes, regardless of the regimen used. Modifications in the regimens, primarily because of intolerance or insufficient antimicrobial coverage of the study drugs, were required in up to one third of episodes in both groups. None of the patients died, and fever disappeared within five days in over 90 percent of all episodes. The most striking difference between the two regimens was that oral therapy was less well tolerated than intravenous therapy. Nonetheless, our finding that the efficacy of the two regimens was equivalent challenges previous assumptions that intravenous delivery of antibiotics is required to achieve a good outcome in patients with fever and neutropenia.

Our definition of low-risk patients was deliberately simple — namely, those in whom the duration of neutropenia was anticipated to be brief (less than 10 days) and who had no other acute medical conditions. The careful selection of a low-risk population was an important factor in the success of the regimens. Fewer than 4 percent of episodes involved a serious medical complication such as cecitis or hypotension.

Other studies have used similar criteria, affirming their predictive value in the setting of fever and neutropenia.^{5-9,16,17} In a benchmark study of risk factors, Talcott et al. found that among febrile outpatients with neutropenia, cancer, and another serious medical condition (uncontrolled pain, nausea, or volume depletion), about half had serious complications, and 14 percent of all patients died.⁵ In contrast, among low-risk outpatients with fever, neutropenia, and cancer but no other serious conditions, they found a 5 percent incidence of complications and no deaths. Our low-risk criteria differed from those of Talcott et al. in that we did not exclude patients with uncontrolled cancer or those who were inpatients at the onset of fever and neutropenia. Nonetheless, we also observed a very low rate of serious medical complications.

The oral regimen produced few adverse effects, other than an inability of patients to tolerate oral administration of ciprofloxacin and amoxicillin-clavulanate in 16 percent of episodes. Diarrhea, a known consequence of treatment with amoxicillin-clavulanate, occurred in 20 percent of episodes in the oral-

TABLE 5. ADVERSE EFFECTS OF EMPIRICAL THERAPY FOR EPISODES OF FEVER AND NEUTROPENIA IN LOW-RISK PATIENTS WITH CANCER.

ADVERSE EFFECT	ORAL CIPROFLOXACIN AND AMOXICILLIN-CLAVULANATE		INTRAVENOUS CEFTAZIDIME	
	TOTAL NO. OF EPISODES	NO. OF EPISODES IN WHICH EFFECT LED TO EARLY WITHDRAWAL	TOTAL NO. OF EPISODES	NO. OF EPISODES IN WHICH EFFECT LED TO EARLY WITHDRAWAL
Diarrhea*	23	1	4	0
Nausea and vomiting*	9	9	3	0
Transient creatinine elevation	1	0	0	0
Rash	1	1	1	1
Total	34	11	8	1

*Episodes were included only if diarrhea, nausea, and vomiting were considered to be related to the study medications.

therapy group but led to the discontinuation of treatment in only one of these episodes. High doses of ciprofloxacin (30 mg per kilogram per day) did not appear to affect the joints of the children who were enrolled in the study.¹⁸⁻²⁰

We analyzed the data before and after the treatment assignments were revealed in order to evaluate the success of intravenous ceftazidime without confounding by any associated intolerance of an oral placebo. We believe that this modification permitted us to view the data in a clinically relevant way, taking into account the complexity of double-blind comparisons of oral and intravenous drugs. The double-blind, placebo-controlled design allowed unbiased decision making throughout the study. Nonetheless, this approach may have introduced some bias against intravenous therapy, since it allowed a longer period of intravenous treatment during which modifications could be made. Modifications in the regimens were considered to indicate treatment failure. However, in an analysis of the blinded data in which this bias was removed, and all instances of intolerance of oral study drug were considered to indicate treatment failure, the rate of success was 71 percent in the oral-therapy group and 59 percent in the intravenous-therapy group ($P=0.07$). Thus, regardless of the method of analysis, our findings indicate that oral antibiotics are at least as efficacious as intravenous ceftazidime as empirical therapy for fever and neutropenia.

It is critical to emphasize that we excluded high-risk patients from the study. In evaluating the appropriateness of oral therapy in febrile patients with cancer and neutropenia, physicians must rigorously exclude any who have another underlying condition and those in whom neutropenia is expected to be prolonged, since these factors could adversely affect the outcome. Furthermore, all our patients remained hospitalized until the fever and neutropenia resolved. Although our findings affirm the safety of inpatient treatment with oral antibiotics, more studies are required to guide the use of oral regimens for fever and neutropenia in outpatients. Several open-label studies have tried oral antibiotic therapy in outpatients, either initially or after a short period of observation in the hospital.^{6-9,16,17,21-23} However, questions remain regarding patients' medical, psychological, and social suitability for outpatient therapy, and there are no guidelines regarding the frequency and nature of medical follow-up.

Our findings underscore the usefulness in patients who have fever and neutropenia as a result of cancer chemotherapy of a risk-assessment approach that is based on prognostic factors that can be easily identified by primary care oncologists. This simplified approach may ultimately result in substantial

cost savings and an improved quality of life for these patients.

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