Comparative efficacy and toxicity of moxalactam and the combination of nafcillin and tobramycin in febrile granulocytopenic patients[1]

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Moxalactam was compared with the combination of nafcillin and tobramycin as empiric therapy for 86 patients who experienced 108 episodes of granulocytopenia and fever. Fifty-three patients received moxalactam (group I), and 55 were given nafcillin and tobramycin (group II). Most of the patients had acute leukemia or lymphoma. A clinically documented infection was present in 76.4% of the patients in group I and in 71.9% of those in group II. Microbiologically documented infections were present in 64.2% and 54.5%, respectively. *Escherichia coli*, *Staphylococcus aureus*, and *Klebsiella pneumoniae* were the most common pathogens; *Pseudomonas aeruginosa* was seventh in frequency. The response rates were 67.4% in group I and 64.5% in group II, with elimination of the pathogen in 78.5% and 65.4%, respectively. Nephrotoxicity and skin rash were significantly more frequent in group II patients. We conclude that moxalactam may be an effective, safe therapy for febrile, granulocytopenic patients in hospitals in which *P. aeruginosa* is an uncommon pathogen.

Index terms: Agranulocytosis • Antibiotics • Infection
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Bacterial infections are a common occurrence and the leading cause of death in granulocytopenic cancer patients, particularly those with hematologic malignancies.[1–6]

Although the early administration of broad-spectrum antibiotic therapy has resulted in an improved prognosis for such patients, superinfection produced by resistant bacteria and fungi and untoward effects associated with the use of antimicrobial agents with a low therapeutic-to-toxic ratio, such as the aminoglycosides, remain significant problems.[7–12]

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The use of more aggressive chemotherapeutic agents has resulted in longer periods of bone marrow suppression and the potential for an increased incidence of untoward reactions in such patients.

An antipseudomonal penicillin and an aminoglycoside antibiotic have been administered initially in most instances of granulocytopenia and fever, and therapy has been continued until the infection has been eliminated and/or the granulocytopenia has resolved.[13] Adjustments in such empiric antimicrobial regimens have been based on the results of cultures and the patient's response to therapy.

The choice of antibiotic therapy for granulocytopenic, febrile patients has been based on the apparent increased susceptibility of such individuals to serious gram-negative infections[8] and in vitro evidence suggesting synergistic bacterial activity against certain aerobic gram-negative bacilli, such as *Pseudomonas aeruginosa*, when two or more antibiotics, usually an antipseudomonal penicillin and an aminoglycoside, are combined.[7,8,10] However, it has not been established conclusively that such regimens are more effective in vivo than nonsynergistic combinations or than single broad-spectrum antibiotics.[10,14–16] Furthermore, recent observations suggest that the cause of bacterial infections in granulocytopenic cancer patients has changed in some hospitals, with a decline in the frequency of *Pseudomonas* isolates and an increase in the isolation of gram-positive cocci, particularly *Staphylococcus aureus*.[13,17–22]

Microbiologic surveillance of patients admitted to the Hematology-Oncology service at the Cleveland Clinic Hospital has demonstrated that staphylococcal infections are notably more prevalent than infections produced by *P. aeruginosa* (*Table 1*). Other species more frequently isolated than *P. aeruginosa* include *Escherichia coli*, *Klebsiella* species, *Serratia marcescens*, and *Enterobacter cloacae*. For this reason, the standard therapeutic program utilized for granulocytopenic febrile patients at our hospital has consisted of administration of the combination of a penicillinase-resistant penicillin, nafcillin, and an aminoglycoside, tobramycin.

Table 1. Bacteremia in cancer patients, The Cleveland Clinic Foundation (Oct 1980 to July 1982)

Bacteria	Number of strains	Percent
Escherichia coli	41	20.2
Klebsiella pneumoniae	32	15.8
Staphylococcus epidermidis	29	14.3
Staphylococcus aureus	17	8.4
Serratia marcescens	14	6.9
Enterobacter cloacae	13	6.4
Klebsiella oxytoca	8	3.9
Pseudomonas aeruginosa	7	3.4
Citrobacter species	6	3.0
Others*	36	17.7
TOTAL	203	100.0

* No single species isolated more than twice.

Moxalactam, a beta-lactam antibiotic, is highly active in vitro against most gram-negative bacilli, many gram-positive cocci, and the majority of pathogenic anaerobic bacteria.[23,24] When administered in appropriate doses, moxalactam has been effective against infections produced by such species.[25–27] With the exception of hypersensitivity reactions in penicillin- or cephalosporin-allergic patients, untoward effects associated with the use of moxalactam have been infrequent and easily correctable, seldom requiring discontinuation of therapy.[25–27]

We conducted a prospective, randomized, controlled trial from October 1980, to August 1982, in order to compare the efficacy and toxicity of moxalactam, used as a single agent, with a combination of nafcillin and tobramycin in the empiric therapy of suspected infection in patients with granulocytopenia and fever.

Materials and methods

Criteria for entry into the study included the presence of an absolute granulocyte count of 1000 or fewer cells/mm^3, a fever of at least 38°C on two or more occasions during a period of 24 hours (or one single temperature elevation of 38.5°C) not associated with the transfusion of blood products, and the absence of a history of immediate hypersensitivity reactions to penicillin or other beta-lactam antibiotics. Patients were excluded if they had received antibiotics within 48 hours prior to consideration for entry into the study.

After signed informed consent had been obtained, randomization was carried out by selecting a sealed envelope containing the description and dosage of the antibiotic regimen to be employed. Neither the patients, the investigators, nor the primary physicians were aware of the information contained in each envelope.

Surveillance cultures, complete blood count, chest radiograph, serum electrolytes, and tests of

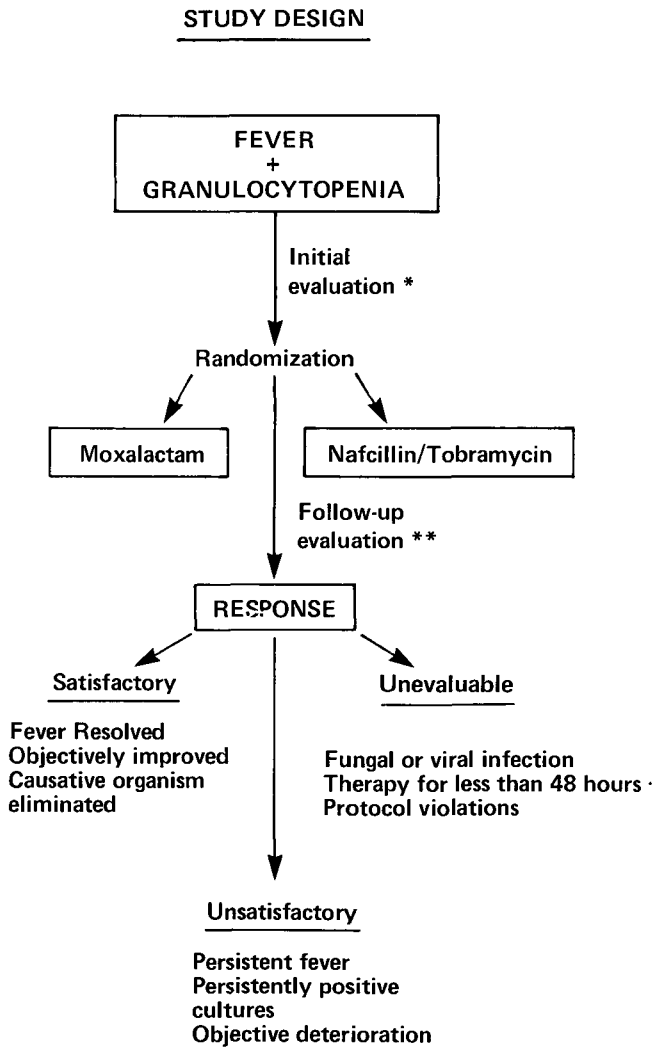
renal, hepatic, and clotting function were obtained prior to administration of the antibiotics and at least weekly therafter (*Figure*). Cultures were obtained from all potential sites of infection, and, when unrevealing, a tissue diagnosis of infection was aggressively pursued. A complete history and physical examination and daily follow-up visits were carried out by one of the investigators. A sputum culture and Gram stain were obtained in patients with signs, symptoms, or radiologic evidence of pulmonary infection. If sputum could not be obtained, more invasive procedures, including bronchoscopic examination and open-lung biopsy, were carried out as permitted by the patient's clinical condition.

Each antibiotic dose was mixed in a 100-ml solution of 5% dextrose in water and administered intravenously for 15–30 minutes. Moxalactam was administered at a dose of 200 mg/kg/day, with a maximal dose of 14 g/day, at six- or eight-hour intervals. The doses of nafcillin and tobramycin were 200 mg/kg/day (maximal dose, 12 g/day, at four-hour intervals) and 5 mg/kg/day (1.7 mg/kg every eight hours), respectively. Modifications in the dosage and time interval of tobramycin administration were made as necessary, based on the serum creatinine and serum concentrations of the antibiotic.

Febrile episodes were classified according to the criteria of Schimpff et al[7] as: (1) microbiologically documented: a pathogen identified, with or without associated bacteremia; (2) clinically documented: a site of infection identified, but with sterile cultures; and (3) fever of unknown origin: fever present, without an obvious site of infection and with sterile cultures. Antibiotics were administered until resolution of granulocytopenia and fever, the development of an adverse reaction, or isolation of a pathogen resistant to the antibiotic being administered.

Patients in whom colonization or infection with *Candida albicans* was clinically suspected or microbiologically confirmed received oral nystatin at regular intervals. Clinically or endoscopically proved *Candida* esophagitis was treated by the administration of amphotericin B, 0.1–0.2 mg/kg/day, in most instances. Some patients received oral ketoconazole, 200 mg/day.

Amphotericin B, administered intravenously, at a dose of 0.5 mg/kg/day, was administered empirically for the therapy of suspected systemic fungal infection to patients in whom fever persisted for more than seven days despite antibiotic therapy, and in whom no evidence of localized or systemic infection could be detected.



Study design.

* Complete history and physical examination, chest radiograph, complete blood cell count (CBC) with differential white blood cell count, chemistry profile (serum electrolytes, renal and liver function tests, glucose, uric acid, cholesterol, creatine phosphokinase, and lactic dehydrogenase), prothrombin time, partial thromboplastin time, and aerobic, anaerobic, and fungal cultures of blood, sputum, throat, urine, and other sites ("surveillance" cultures).

** Daily physical examinations; twice weekly: CBC, chemistry profile, chest radiograph, and "surveillance" cultures; weekly: prothrombin time and partial thromboplastin time.

Antibiotic responses were classified as follows: (1) successful: disappearance of fever and resolution of clinical and bacteriologic (when available) evidence of infection; (2) successful with recurrence: when, after a successful response, there was recurrence of fever, signs of localized or systemic infection, or cultures yielding the

organism initially isolated; (3) failure: no clinical response, persistent objective and microbiologic (when available) evidence of infection, or the organism isolated was resistant to the antibiotic regimen employed; (4) nonevaluable: insufficient clinical information, fungal or viral infections were present, or violations of the protocol prevented interpretation of the patient's clinical course.

Superinfection was defined as any infection, produced by an organism not present in the initial cultures, which developed during the antibiotic therapy or, in patients in whom antibiotics were no longer being administered, for the duration of the hospitalization. Colonization was defined as the isolation, during or following therapy, of microorganisms not present in the pretreatment cultures but not responsible for the production of clinical infection.[28]

Drug rash was defined as a morbilliform or maculopapular skin eruption developing in any patient immediately after the initiation, during the course, or within one week following discontinuation of antibiotics. Nephrotoxicity was defined according to the criteria of Smith et al[29] as an increase in the serum creatinine of ≥ 0.5 mg/1dl when the initial creatinine had been < 3.0 mg/dl or an increase in the serum creatinine of 1.0 mg/dl when the initial creatinine had been ≥ 3.0 mg/dl. Nephrotoxicity was recorded only when all other possible causes of azotemia, including the concomitant administration of amphotericin B, presence of hypotension, or the use of other potentially nephrotoxic drugs, had been excluded. Hypokalemia was considered to be related to antibiotic administration when the serum potassium decreased 1 mEq/L or more from the concentration prior to antibiotic administration, in the absence of diarrhea or concurrent therapy with amphotericin B or diuretics.[30] Coagulopathy was defined as a prolongation of the prothrombin time two seconds or more than the control as compared to the pretherapy value, or as clinical evidence of bleeding developing in the absence of thrombocytopenia (≤ 50,000 platelets/hpf).

The statistical analysis was carried out by chi-square analysis and by the one-sided Fisher's exact test with a level of significance of 0.05 to compare differences in proportions. The Yates correction was used when necessary.

Results

Eighty-six patients who experienced 108 episodes of granulocytopenia and fever were studied. Moxalactam was administered in 53 episodes (group I), and nafcillin and tobramycin were used in 55 episodes (group II).

Patient characteristics: Both groups of patients were comparable with regard to sex, age, race, and weight (*Table 2*). Three patients in group I had a history of possible hypersensitivity to pen-

Table 2. Patient characteristics (dose and duration of therapy)

	Moxalactam	Nafcillin	Tobramycin	Statistical significance*
Episodes	53	55		
Sex Male	28 (52.8%)	27 (49.1%)		NS
Sex Female	25 (47.2%)	28 (50.9%)		
Mean age (years)	47.4	46.2		NS
range	9–74	15–74		
Race Black	8 (15.1%)	8 (14.5%)		NS
Race White	45 (84.9%)	47 (85.5%)		
Mean weight (kg)	68.4	69.0		NS
range	29–102	39–114		
Allergies Penicillin	3	2		NS
Allergies Other	8	8		
Mean daily dose (mg/kg/day)	193.5	184.6	4.8	
range	53–254	105–240	(3.1–5.7)	
Dose interval	6 (31)	4 (55)	8 (54)	
Hours (no. courses)	8 (22)		10 (1)	
Mean duration (days)	8.2†	8.1†		
range	2–19	1–21		

* Chi-square analysis with Yates correction.
† P > 0.05, chi-square analysis.
NS = Not significant.

icillin. Eight additional patients had histories of other drug allergies. Two patients in Group II were allergic to penicillin, and 8 had other allergies. None of the penicillin-allergic patients had histories of immediate hypersensitivity to this antibiotic.

Acute leukemia was the primary disease in 52.8% of the patients in group I and in 67.3% of those in group II (*Table 3*). Other hematologic malignancies, such as lymphomas and solid tumors, were equally prevalent in both groups. Three patients had granulocytopenia unrelated to the presence of a malignancy.

The average dose of the antibiotics and the length of therapy are described in *Table 2*. For group I, a mean daily dose of 193.5 mg/kg/day of moxalactam was given every six hours (31 patients) or eight hours (22 patients). In group II, nafcillin was administered at a mean daily dose of 184.6 mg/kg/day, at four-hour intervals, and tobramycin at a dose of 4.8 mg/kg/day, in three equally divided doses, or as frequently as required, based on the degree of renal dysfunction. The duration of therapy in both groups was comparable.

Temperature; duration and depth of granulocytopenia: Temperature on entry into the study and the duration and degree of granulocytopenia were comparable for both groups (*Table 4*). The mean temperature in group I patients was 38.9°C and 39.0°C in group II patients. The mean granulocyte count at the time of entry into the study was 245.9 cells/mm^3 for group I and 165.3 cells/mm^3 for group II. The absolute granulocyte count fell below 100 cells/mm^3 in 71.7% of the patients given moxalactam and in 78.2% of those who received nafcillin and tobramycin. The mean duration of granulocytopenia was 16.3 days for group I and 18.2 days for group II. The duration of granulocytopenia was longer than the duration of antibiotic therapy in many instances because fever did not develop coincident with the appearance of granulocytopenia in some patients.

Twenty-three patients (43.4%) in group I and 25 (45.5%) in group II received granulocyte transfusions. The number of granulocyte transfusions, duration of granulocytopenia, and nadir of granulocytopenia were comparable in both groups. The decision to administer granulocyte transfusions was made in all cases by the primary physician. In general, patients receiving granulocyte transfusions had a longer duration and a greater degree of granulocytopenia than patients who did not receive transfusions of white blood cells. Although the presence of bacteremia was the single most important indication for granulocyte transfusions, patients were given granulocyte transfusions empirically in some instances when fever persisted or clinical deterioration was evident.

Table 3. Primary disease*

Disease	Moxalactam (No. of episodes)	Nafcillin/ tobramycin (No. of episodes)	Statistical significance†
Acute leukemia	28 (52.8%)	37 (67.3%)	NS
Lymphoma	13 (24.5%)	11 (20%)	NS
Solid tumors	9 (17%)	7 (12.7%)	NS
Aplastic anemia	3 (5.7%)	0 (0%)	NS

* Eleven patients (6 in the moxalactam group and 5 in the nafcillin/tobramycin group) underwent bone marrow transplantation.
† Chi-square analysis.
NS = Not significant.

Clinical diagnosis: Table 5 displays the diagnosis made in the 108 episodes of granulocytopenia and fever. A specific infection was identified in 73% of the episodes in both groups, whereas 27% of the episodes were classified as fevers of unknown origin.

Bacteremia was equally prevalent in both groups, occurring in 16.4% of the patients in group I and in 21% of the patients in Group II ($P > 0.05$). There were no significant differences in the incidence of pneumonia, mucositis, or cutaneous, gastrointestinal, or upper respiratory tract infections.

Table 4. Temperature and granulocytopenia

	Moxalactam	Nafcillin/ tobramycin	Statistical significance*
Mean temperature on entry (range)	38.9°C (38°C–40.5°C)	39.0°C (38°C–40.8°C)	NS
Mean initial granulocyte count (range)	245.9 (0–1410)	165.3 (0–1127)	NS
Nadir of granulocytopenia			
≤100 cells/mm^3	38 (71.7%)	43 (78.2%)	NS
101–500 cells/mm^3	14 (26.4%)	11 (20.0%)	NS
>500 cells/mm^3	1 (1.9%)	1 (1.8%)	NS
Duration of granulocytopenia	16.3 days	18.2 days	NS
1–5 days	9 (17.0%)	6 (10.9%)	NS
6–10 days	14 (26.4%)	15 (27.3%)	NS
>10 days	30 (56.6%)	34 (61.8%)	NS

* Chi-square analysis and Fisher's exact test.
NS = Not significant.

Table 5. Clinical diagnosis on entry

Diagnosis	Moxalactam (No. of episodes)	Nafcillin/tobramycin (No. of episodes)	Statistical significance*
Fever of unknown origin	13 (23.6%)	16 (28.1%)	NS
Bacteremia	9 (16.4%)	12 (21.0%)	NS
Skin infection	7 (12.7%)	7 (12.3%)	NS
Gastrointestinal	7 (12.7%)	6 (10.5%)	NS
rectal abscess	2	4	
Mucositis	6 (10.9%)	6 (10.5%)	NS
Pneumonia	5 (9.1%)	6 (10.5%)	NS
Urinary tract	4 (7.3%)	3 (5.3%)	NS
Upper respiratory	4 (7.3%)	1 (1.8%)	NS

Two patients in each group had two simultaneous infections.
* Chi-square analysis with Yates correction.
NS = Not significant.

Symptoms at the time of entry into the study were similar in both groups. Nonspecific symptoms, such as chills, weakness, malaise, fatigue, nausea, and vomiting, were most frequently observed.

Bacterial isolates: Microbiologic evidence of infection was demonstrated in 64.2% of the patients in group I and in 54.5% of the patients in group II (*Table 6*). The majority of the microbiologically documented infections were bacterial in etiology. *E. coli* and *S. aureus* were most commonly isolated, followed in frequency by *Klebsiella* species, nonenterococcal streptococci, *E. cloacae*, and *P. aeruginosa* (*Table 7*).

Antibiotic susceptibilities of the bacterial isolates are demonstrated in *Table 8*. Sensitivities were available for 42 of the 51 isolates in the moxalactam group. Of these, 36 were susceptible to moxalactam and 37 to nafcillin and/or tobramycin. The six organisms resistant to moxalactam included enterococci (two instances), *P. aeruginosa* (two instances), *Pseudomonas putida*, and *Bacillus cereus* (one instance each). All of these organisms were sensitive to nafcillin and/or tobramycin.

Susceptibilities were available for 43 of the 47 organisms isolated from the patients treated with

Table 6. Microbiologically documented infection

	Moxalactam	Nafcillin/tobramycin	Statistical significance*
Number of episodes	53	55	
Bacterial	30 (56.5%)	29 (52.7%)	NS
Fungal	4 (7.6%)	1 (1.8%)	NS
TOTAL	34 (64.2%)	30 (54.5%)	NS

* Chi-square analysis.
NS = Not significant.

Table 7. Microbial isolates

Organism	Moxalactam	Nafcillin/tobramycin	Total
Escherichia coli	9	10	19 (19.4%)
Staphylococcus aureus	11	6	17 (17.4%)
Klebsiella species	4	7	11 (11.2%)
Nonenterococcal streptococci	5	6	11 (11.2%)
Miscellaneous gram-negative bacilli	3	7	10 (10.2%)
Enterobacter cloacae	4	4	8 (8.2%)
Pseudomonas aeruginosa	4	4	8 (8.2%)
Candida albicans	6	1	7 (7.1%)
Enterococcus	2	1	3 (3.1%)
Staphylococcus epidermidis	1	1	2 (2.0%)
Gram-positive bacilli	2	0	2 (2.0%)
TOTAL	51	47	98 (100%)

nafcillin and tobramycin. Forty-two were susceptible to nafcillin and tobramycin and 40 to moxalactam. The organism that demonstrated resistance to nafcillin and/or tobramycin was a strain of *E. coli* susceptible to moxalactam.

Bacteriologic response: A satisfactory bacteriologic response was observed in 72.2% of the patients with microbiologically documented infection (*Table 9*). In 22 of the 28 evaluable patients (78.5%) in group I in whom bacterial infection was documented, subsequent cultures of the same site were sterile. Eradication of the infecting organism was accomplished in 17 of 29 patients in group II (65.4%).

Moxalactam was effective in the eradication of infection in a number of instances when the bacterial isolate was reported to be resistant to this compound. A possible explanation for this observation is related to a change in the microbiologic criteria for moxalactam susceptibility. In

Table 8. Antimicrobial susceptibility in microbiologically documented infections

	Moxalactam	Nafcillin/tobramycin
Number of documented infections	34	30
Single organism	23	20
Mixed organism	11	10
Number of organisms	51	47
Susceptibility available	42	43
Sensitive to ≤64 μg/ml of moxalactam	36 (85.7%)	40 (93.02%)
Sensitive to ≤2 μg/ml of nafcillin and/or ≤2 μg/ml of tobramycin	37 (90.24%)	42 (97.67%)

Table 9. Bacteriologic response in documented infection

	Moxalactam	Nafcillin/ tobramycin	Statistical significance*
Number (evaluable)	30 (28†)	29 (26‡)	NS
Pathogen eliminated	22 (78.5%)	17 (65.4%)	NS
Pathogen not eliminated	6 (21.5%)	9 (34.6%)	NS
Resistant	4	2	NS
Susceptible	2	7	NS

* Chi-square analysis and Fisher's exact test.
† Two patients excluded because of protocol violations.
‡ Three patients excluded because of protocol violations.
NS = Not significant.

1980, when the study was initiated, a microorganism whose MIC was greater than 16 μg/ml was considered to be resistant to moxalactam. Subsequently, in October 1981, the "breakpoint" between moxalactam susceptibility and resistance was changed to 64 μg/ml. Possibly some of the organisms whose sensitivities were initially reported to be greater than 16 μg/ml may, in fact, have been sensitive to moxalactam at concentrations of 32 or 64 μg/ml, since the majority of these organisms were isolated from patients entered into the study before October 1981. Unfortunately, these bacteria were not available for retesting.

Clinical response: Evaluation of the clinical response was possible in 94 episodes. Evaluation was not possible in 14 instances (7 in group I and 7 in group II) because of significant protocol violations (5 patients), a duration of therapy of 48 hours or less (5 patients), and insufficient clinical information (4 patients).

The clinical response to therapy is displayed in *Table 10*.

Moxalactam was effective in 67.4% and the combination of nafcillin and tobramycin in 64.5% of patients with clinically documented infection. Recurrences were more commonly seen in the latter group (20.8%) than in the former (10.9%) (*Table 10*), but this difference was not statistically significant. Unsatisfactory responses were observed in approximately one third of the cases.

Table 10. Clinical response (94 evaluable cases)*

	Moxalactam (No. of episodes)	Nafcilin/ tobramycin (No. of episodes)	Total
Satisfactory	31 (67.4%)	31 (64.5%)	62 (66%)
Recurrence	5	10	15
Failure	15 (32.6%)	17 (35.5%)	32 (34%)
TOTAL	46 (100%)	48 (100%)	94 (100%)

* Seven cases in each group unevaluable.
$P > 0.05$ for each group, chi-square analysis.

Table 11. Response to therapy of patients with profound granulocytopenia (<100/mm^3)

Duration of profound granulocytopenia	Moxalactam	Nafcillin/ tobramycin	Statistical significance*
1–7 days	10/14 (71.4)	10/14 (71.4)	NS
8–14 days	4/11 (36.4)	9/17 (52.9)	NS
>14 days	6/9 (66.7)	6/11 (54.5)	NS
TOTAL	20/34 (58.8)	25/42 (59.5)	NS

* Chi-square analysis.
NS = Not significant.

Moxalactam was effective in 58.8% of those in whom the total granulocyte count fell below 100 cells/mm^3. The combination of nafcillin and tobramycin was effective in 59.5% of these patients (*Table 11*). The response rates among profoundly granulocytopenic (<100/cells/mm^3) patients with bacteremia were similar (*Table 12*). Satisfactory responses were observed in 6 of 14 bacteremic patients who received moxalactam and in 10 of 21 who received nafcillin and tobramycin.

Adverse reactions: When patients concomitantly receiving nephrotoxic drugs, such as amphotericin B, were excluded, nephrotoxicity was significantly more frequent in group II than in group I (*Table 13*). Significant elevation of the blood urea nitrogen (BUN) and serum creatinine developed in 11 instances in which nafcillin and tobramycin were administered to 10 patients (one patient received nafcillin and tobramycin on two occasions). The duration of tobramycin therapy appeared to be longer in the 11 patients who developed nephrotoxicity than in those who did not. Azotemia necessitated peritoneal dialysis or hemodialysis in 2 of these patients.

Three of the 11 patients had received previous courses of therapy with aminoglycosides. One patient had received tobramycin for five days within a month before entry into the study, one

Table 12. Response to therapy of patients with profound granulocytopenia and bacteremia

Duration of profound granulocytopenia	Moxalactam	Nafcillin/ tobramycin	Statistical significance*
1–7 days	1/2 (50)	3/4 (75)	NS
8–14 days	2/8 (25)	2/8 (25)	NS
>14 days	3/4 (75)	5/9 (55.5)	NS
TOTAL	6/14 (42.8)	10/21 (47.6)	NS

* Chi-square analysis and Fisher's exact test.
NS = Not significant.

Table 13. Adverse reactions (44 patients)

Reaction	Moxalactam (No. of episodes)	Nafcillin/tobramycin (No. of episodes)	Statistical significance*
Nephrotoxicity	1 (1.8%)	11 (20%)	$P < 0.05$
Skin rash	1 (1.8%)	8 (14.5%)	$P < 0.05$
Coagulopathy	10 (18.9%)	4 (7.3%)	NS
Positive Coombs' test	4 (7.5%)	0 (0%)	NS
Diarrhea	3 (5.7%)	4 (7.3%)	NS
Abnormal liver function	4 (7.5%)	3 (5.5%)	NS
Electrolyte imbalance	0 (0%)	4 (7.3%)	NS
Sensory (taste) disturbance	2 (3.8%)	1 (1.8%)	NS
Ototoxicity	0 (0%)	1 (1.8%)	NS
TOTAL PATIENTS	19 (35.8%)	25 (45.5%)	NS

* Chi-square analysis and Fisher's exact test.
NS = Not significant.

had received tobramycin for seven days one month before entry, and the other had received two previous courses six months and one month prior to entry. The azotemia was mild in these 3 patients, and none required hemodialysis or peritoneal dialysis. Hypomagnesemia attributed to tobramycin developed in 2 patients, and hypokalemia developed in 2 patients receiving nafcillin and tobramycin. There were no instances of hypomagnesemia or hypokalemia in patients treated with moxalactam.

Hematologic reactions were observed more commonly in group I: 10 patients (18.9%) had an abnormally prolonged prothrombin time, and 4 had a positive Coombs' reaction. The administration of nafcillin and tobramycin was associated with prolongation of the prothrombin time in 4 patients. No group II patients developed a positive Coombs' reaction. Differences in the incidence of hematologic reactions were not statistically significant.

All patients with prolonged prothrombin times responded within 24 hours to the administration of vitamin K. Vitamin K was administered subcutaneously to these patients because the coagulopathy precluded deep intramuscular injections, and intravenous administration was considered too hazardous. None of the patients with a prolonged prothrombin time had clinical evidence of bleeding, and there was no bleeding at the site of the subcutaneous injection.

None of the patients with a positive Coombs' test developed hemolysis. In 3 patients, the reaction was interpreted as "weakly positive," and subsequent testing in one demonstrated disappearance of the positive reaction. The reaction was "moderately positive" in the fourth patient, and therapy with moxalactam was terminated. A Coombs' test performed after discontinuance of moxalactam was negative.

Skin rash developed significantly more frequently in the patients treated with nafcillin and tobramycin. Other adverse reactions, including diarrhea, a bitter aftertaste, and elevated transaminases and total bilirubin, occurred with equal frequency in both groups. All of the patients with abnormal liver function had received potentially hepatotoxic drugs, such as cytosine arabinoside, immediately before or concomitant with the administration of the antibiotics.

Table 14. Incidence of superinfection, colonization, and relapse of infection

	Moxalactam (No. of episodes)	Nafcillin/tobramycin (No. of episodes)	Statistical significance*
	53	55	
Superinfection	5 (9.4%)†	8 (14.5%)‡	NS
Probably related§	3	6	NS
Possibly related‖	2	2	NS
Colonization	13 (24.5%)	8 (14.5%)	NS
Enterococcus	5	0	$P < 0.05$
Enterococcus and *Candida albicans*	5	1	NS
C. albicans	2	7	NS
C. albicans and *Torulopsis glabrata*	1	0	NS
Relapse of previously documented infection	2 (3.8%)	2 (3.6%)	NS

* Chi-square analysis.
† Three fungal, 2 bacterial (1 enterococcus, 1 nonenterococcal streptococcus).
‡ Five with multiresistant gram-negative bacilli.
§ Developed during or within one week of discontinuation of study drugs; no other antimicrobial agents used.
‖ Developed after one week or longer of discontinuation of study drugs or while other antimicrobial agents were being administered.
NS = Not significant.

Superinfection, colonization, and relapse of infection: Superinfection was documented in 13 patients, 5 in group I and 8 in group II. Colonization developed in 13 patients in group I and in 8 patients in group II; relapse of an infection developed in 2 patients treated with moxalactam and in 2 treated with nafcillin and tobramycin (*Table 14*).

Three patients in group I had fungal infections: 2 had disseminated aspergillus infection, and one had *Torulopsis glabrata* gastroenteritis; one had enterococcal bacteremia, and one had nonenterococcal streptococcal bacteremia. Both

patients with disseminated aspergillus infection died.

In group II, 4 of the 8 patients developed superinfection with multiresistant gram-negative bacilli (*E. coli* bacteremia in 2, *S. marcescens* bacteremia in one, and *Klebsiella oxytoca* bacteremia in the fourth). Three patients had superinfection with tobramycin-susceptible organisms: *S. marcescens* bacteremia in one, *Acinetobacter lwoffi* bacteremia in one, and *K. oxytoca* bacteremia in the third. One patient developed *Fusobacterium* species bacteremia and died six days following discontinuation of nafcillin and tobramycin therapy.

Colonization was detected in 13 patients receiving moxalactam. Five patients were colonized with enterococci, 5 with enterococci and *C. albicans*, 2 with *C. albicans*, and one with *C. albicans* and *T. glabrata*. Eight patients receiving nafcillin and tobramycin developed colonization. Seven of these were colonized with *C. albicans* and one with *C. albicans* and enterococci.

Four patients suffered a relapse from a previously documented infection. One patient was a 29-year-old man with acute leukemia in whom a previous course of cefamandole had been associated with the development of *Clostridium difficile*-associated pseudomembranous colitis. He became asymptomatic, and repeated stool examinations failed to reveal *C. difficile* or its toxin after seven days of therapy with oral vancomycin. The patient developed fever shortly after the discontinuation of oral vancomycin. Since he was granulocytopenic when the fever developed, he was entered into the study and received moxalactam. Urine cultures revealed a urinary infection with *E. coli*. Three days later diarrhea developed, and there was a high cytotoxic toxin titer of *C. difficile* in the fecal filtrate. Moxalactam was discontinued; the patient recovered after a course of oral vancomycin.

The second patient was a chronic gastrointestinal carrier of *Salmonella newport*. Prior to development of granulocytopenia, she had received a two-week course of parenteral ampicillin because of fever, leukocytosis, and positive stool cultures. She responded adequately, with resolution of fever and eradication of *S. newport* from the stool. However, after 13 days of moxalactam therapy, administered when she became granulocytopenic and febrile, diarrhea developed. Stool cultures yielded *S. newport* with susceptibilities identical to those of the strain isolated earlier in her hospitalization. The organism was highly susceptible to moxalactam (MIC $\leq$ 0.25 μg/ml).

Two patients receiving nafcillin and tobramycin experienced relapse of an infection. A 59-year-old woman with acute myelogenous leukemia had polymicrobial bacteremia with *K. oxytoca*, *Citrobacter freundii*, *E. coli*, and *Klebsiella pneumoniae*. She received nafcillin and tobramycin, and the blood cultures became sterile. However, after six days of therapy, the blood cultures again yielded *K. oxytoca*. She subsequently responded to moxalactam.

A 65-year-old man with chronic granulocytic leukemia had a rectal abscess and received nafcillin and tobramycin for 16 days. Cultures of the rectal abscess had yielded *E. coli* as the predominant organism. The infection remained "contained," and there were no positive blood cultures during therapy. However, three days after the antibiotic had been discontinued, *E. coli* bacteremia returned and persisted until his death.

Discussion

Combinations of antibiotics have been recommended as the therapy of choice for granulocytopenic cancer patients in whom bacterial infection, as manifested by the development of fever, is suspected. Although such combinations have been demonstrated to produce synergistic effects against *P. aeruginosa* and other aerobic gram-negative bacilli in vitro, there is conflicting information concerning whether they are superior to nonsynergistic or single-drug regimens in vivo. Furthermore, such combinations usually include an aminoglycoside antibiotic, a potential nephrotoxin and ototoxin.[9,10,14,15]

The extended spectra of activity of the newer beta-lactam antibiotics, especially against microorganisms not susceptible to the aminoglycosides and to some of the penicillins, has provided the opportunity to achieve broad-spectrum antimicrobial activity with compounds not associated with the potential for the production of ototoxicity and/or nephrotoxicity.

Recent reports[16–22] have drawn attention to a change in the bacterial etiology of infections in severely granulocytopenic cancer patients, and have emphasized both the increasing importance of infections produced by staphylococcal species and a decline in those produced by *P. aeruginosa*. We have observed a similar phenomenon. *E. coli*, *K. pneumoniae*, *S. epidermidis*, and *S. aureus* are the four most frequent bloodstream isolates in cancer patients in our hospital, and *P. aeruginosa* accounts for only 3.3% of the instances of bacteremia in these patients.

Although moxalactam is somewhat less active than cephalosporins and penicillins against most gram-positive cocci, we observed that this antibiotic was effective in the eradication of infection in 100% of patients in whom *S. aureus* was isolated. These findings are consistent with those of others, who have demonstrated that, at high dose, due to the achievement of high serum concentrations that can be achieved, moxalactam may be effective in the management of infections produced by *S. aureus.*[31–34]

Moxalactam is highly active against the majority of aerobic gram-negative bacilli, but concern has been raised regarding the use of this compound as a primary antipseudomonal agent since in vitro studies have demonstrated that only 60% to 75% of *P. aeruginosa* isolates are susceptible to 16 μg/ml of moxalactam.[23,24] At least four of the eight strains of *P. aeruginosa* isolated from our patients were susceptible to moxalactam (MIC ≤ 16 μg). All of the strains were susceptible to tobramycin.

In this randomized, prospective study, moxalactam was as effective as the combination of nafcillin and tobramycin in the treatment of febrile, granulocytopenic patients. Recently, it has been noted that the degree of granulocytopenia is an important factor in determining the outcome of infections and the efficacy of antimicrobial therapy.[34] Patients with granulocyte counts below 100/mm^3 appear to be at greatest risk for unsatisfactory results. The response rates of profoundly granulocytopenic patients in this study were lower than those of other patients. However, there was no significant difference in the efficacy of moxalactam and the combination of nafcillin and tobramycin.

This study demonstrated a low incidence of untoward effects in patients receiving moxalactam and a significantly lower incidence of nephrotoxicity in the moxalactam-treated patients compared with those who received nafcillin and tobramycin. Brown et al[32] previously have demonstrated that therapy of suspected infections with moxalactam was associated with a low incidence of further nephrotoxic damage in patients with solid tumors, who had had frequent exposure to chemotherapeutic agents such as cis-platinum, a known nephrotoxin. The untoward effects associated with the administration of moxalactam were mild and usually clinically insignificant. In those patients in whom prolongation of prothrombin time developed, rapid correction, usually within 24 hours, was achieved following subcutaneous administration of vitamin K, as previously described.[35,36]

Potential hazards associated with the use of broad-spectrum antimicrobial therapy are development of resistance by the infecting organism during the course of therapy and elimination of normal saprophytic microflora of the patient, with subsequent overgrowth of resistant bacteria and fungi. The development of moxalactam resistance during therapy has been reported.[37] However, we observed no instances of moxalactam resistance during treatment.

The frequency of superinfection in patients treated with moxalactam in this study was similar to that observed in patients treated with nafcillin and tobramycin, and was comparable to the incidence of superinfection noted by others when combinations of carbenicillin and gentamicin or carbenicillin, cephalothin, and gentamicin have been employed.[7,9,38]

The use of moxalactam as a single agent for the treatment of febrile, granulocytopenic patients must be based on knowledge of the microorganisms most frequently responsible for the infection. Moxalactam appears to constitute appropriate therapy in hospitals, such as ours, in which *P. aeruginosa* is an uncommon pathogen. In institutions in which the incidence of *Pseudomonas* infection is high, combination therapy with at least two antipseudomonal compounds must continue to be regarded as the therapy of choice until greater clinical experience in the use of single agents is available.

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