ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, May 1992, p. 1062–1067
0066-4804/92/051062-06$02.00/0

Vol. 36, No. 5

Vancomycin Is Not an Essential Component of the Initial Empiric Treatment Regimen for Febrile Neutropenic Patients Receiving Ceftazidime: a Randomized Prospective Study

REUBEN RAMPHAL,[1]* MICHAEL BOLGER,[2] DAVID J. OBLON,[1] ROBERT J. SHERERTZ,[1] JOHN D. MALONE,[2] KENNETH H. RAND,[1] MERCEDES GILLIOM,[2] JOSEPH W. SHANDS, JR.,[1] AND BARNETT S. KRAMER[2]

Department of Medicine, University of Florida, Gainesville, Florida 32610-0277,[1] and National Cancer Institute Navy Medical Oncology Branch, National Naval Medical Center, Bethesda, Maryland 20814[2]

Received 9 December 1991/Accepted 29 February 1992

The use of vancomycin as part of the initial antibiotic therapy of febrile neutropenic patients has become a controversial issue. Some studies support its incorporation in the initial regimen, and others suggest that vancomycin can be added later. We examined this issue in a prospective, randomized trial. We randomized 127 febrile neutropenic patients to receive either ceftazidime alone or ceftazidime plus vancomycin as the initial empiric antibiotic treatment. We added vancomycin to the ceftazidime arm of the study when fever persisted after 96 h of monotherapy, when new fever occurred after this time, or when a moderately ceftazidime-resistant gram-positive bacterium was isolated. Each of these regimens had similar initial response rates, similar durations of initial fever, similar frequencies of new fever during therapy, similar microbiological cure rates, similar superinfection rates, and similar survival rates. We observed more renal and cutaneous toxicities in patients receiving vancomycin and ceftazidime as initial therapy. We conclude that ceftazidime is appropriate as initial therapy for febrile neutropenic patients and that the addition of vancomycin is appropriate when fever persists after 4 days of monotherapy or when fever recurs following an initial response.

The use of vancomycin or a vancomycinlike drug as part of the initial empiric antibiotic treatment for febrile neutropenic patients has become a controversial issue. In 1983, we advocated the use of vancomycin as part of the initial regimen after a trial of ceftazidime monotherapy because we encountered several lethal gram-positive superinfections (12) and we subsequently showed that the addition of vancomycin to ceftazidime abrogated these superinfections (7). Other studies with different antibiotic combinations also supported the need for vancomycin as part of the initial regimen because of the increasing number of gram-positive infections that were being seen as well as for gram-positive superinfections which occurred during therapy (1, 4, 6, 16). However, large studies done by the National Cancer Institute suggested that the addition of vancomycin can be delayed without any resulting increase in morbidity or mortality, even when a gram-positive infection is proven (11, 13). Nevertheless, the issue seems to have remained unsettled, with many recent publications examining the use of vancomycin or a vancomycinlike drug as an empiric addition to one or more drugs for fever and neutropenia (2, 9, 20). The most recent study on this controversy was published by The European Organization for Research and Treatment of Cancer (EORTC) and National Cancer Institute of Canada in a large study of gram-positive infections (17). These organizations used a combination of ceftazidime and amikacin as the standard therapy and concluded that the empiric addition of vancomycin to this regimen was not needed, even though there were statistically significant differences in the responses of clinically documented infections and gram-positive bacteremias in favor of the addition of vancomycin. That study did, however, point out that there was no increased morbidity or mortality involved with the later addition of vancomycin in patients who required it.

It thus appears that both approaches work, but it has never been clear as to what the criteria should be for the use of vancomycin, and suggested criteria have not been tested in a prospective fashion. The present study, which was performed between July 1986 and August 1988, was therefore designed to test certain criteria which resulted from a retrospective analysis of our own data from previously published studies. The criteria tested are outlined below.

MATERIALS AND METHODS

Study design. The study was designed as an unblinded, prospective, randomized trial comparing outcomes with the use of ceftazidime alone versus ceftazidime plus vancomycin as empiric therapy for fever in neutropenic patients. The protocol allowed for the later addition of vancomycin to ceftazidime when indicated, by use of the criteria stated below. The study was conducted at Shands Hospital, University of Florida, Gainesville, and Bethesda Naval Hospital, Bethesda, Md.

Patient entry and management. The study entry criteria were as follows: (i) underlying neoplastic disease; (ii) ≥18 years old; (iii) neutropenia, as defined by an absolute neutrophil-plus-band count of <500/mm^3 or ≤1,000/mm^3 and falling; (iv) and fever, as defined by an oral temperature of ≥38°C on two occasions 6 h apart or ≥38.5°C on one occasion not associated with blood product transfusions. Patients were excluded if they had received parenteral antibiotics in the preceding 96 h or had a known allergy to any of the study drugs. All patients gave written informed consent. Since neutropenia could be anticipated in many patients, informed consent was obtained prior to the onset of fever in most patients. Neither the patient nor the person obtaining informed consent was aware of the treatment

* Corresponding author.

assignment at the time that consent was obtained. Randomization occurred after the onset of fever. Oral prophylactic antibiotics were not used prior to or during the study.

The initial evaluation at entry to the study included the following: (i) two blood samples for cultures taken from different sites, a vein and a Hickman catheter when present; (ii) cultures for samples taken from any site clinically suspected of being infected; (iii) chest roentgenogram; (iv) urinalysis; and (v) serum electrolyte, blood urea nitrogen, creatinine, and liver function tests.

Patients received either ceftazidime alone in a dose of 2 g intravenously every 8 h or ceftazidime in the same dose plus vancomycin in a dose of 1 g every 12 h, according to a 1:1 randomization schedule. Criteria for the addition of vancomycin to the ceftazidime arm of the study were as follows: (i) the isolation from initial or subsequent blood cultures of a gram-positive bacterium which was relatively resistant to ceftazidime (MIC, ≥8 μg/ml); (ii) a fever persistent for 96 h after the initiation of ceftazidime (the earliest gram-positive superinfections were seen after this time in an earlier study [7]); or (iii) a new fever after an afebrile period of at least 48 h with ceftazidime alone. Amphotericin B was added to either arm after 7 days of antibiotic treatment for new or persistent fevers or for a documented fungal infection. Aminoglycosides were added only for the isolation of a ceftazidime-resistant gram-negative bacterium or for a deteriorating clinical condition after 2 weeks of ceftazidime therapy. Patients were monitored until the resolution of neutropenia, at which time the antibiotics were stopped. Blood vancomycin concentrations were monitored, and doses were adjusted to maintain peak concentrations of between 10 and 25 μg/ml. Two sets of blood samples for cultures were drawn on all days when the patients were febrile to monitor for superinfections. Catheter insertion sites or catheter tips were cultured when there was any suspicion of infection. A catheter-associated infection was diagnosed when there was clinical evidence of an infection, pain, redness, and the isolation of an organism from the site or the catheter tip. Other sites were cultured as clinically indicated. Chest X rays were obtained weekly or more frequently when indicated. All bacterial isolates were tested for susceptibility to ceftazidime and/or vancomycin by tube dilution. The occurrence of rashes or increases in creatinine levels was noted for the assessment of drug toxicity.

Evaluation of patients. We examined five parameters to evaluate therapy: (i) initial clinical responses, i.e., the percentage of patients becoming afebrile in each arm within 96 h and remaining afebrile for at least 48 h; (ii) microbiological cure of documented infections in each arm, in this case primary bacteremias or catheter site infections with or without bacteremias; (iii) superinfections; (iv) deaths and their precipitating causes; and (v) survival at resolution of neutropenia and fever. Statistical analyses were done by use of a two-tailed chi-square analysis for outcomes, and comparisons of means were made by use of the Student *t* test or the Wilcoxon rank sum test. Randomization was stratified by institution. Randomization was performed by a computer random-number generator, and individual assignments were kept in the pharmacy of each institution. After the treating physician obtained informed consent from the patient, he or she called the pharmacy for treatment assignment. Sample size was calculated prospectively to detect a 15% difference in survival and superinfection rates between study arms with 80% statistical power (i.e., the prospectively determined beta-error was 0.20, with a two-sided alpha-error of 0.05).

TABLE 1. Patient characteristics

Characteristic	Value for the following study arm:	
	Ceftazidime	Ceftazidime + vancomycin
Total no. of patients	63	64
Sex (males/females)	35/28	38/26
Median age (range), in yr	40.0 (18–83)	41.0 (18–76)
No. (%) with acute leukemia	44 (70)	35 (55)
Mean neutrophil count/mm^3 on entry (range)	60 (0–1,000)	70 (0–1,000)
No. of days neutropenic		
Mean	13.6 ± 10	12 ± 11
Median (range)	12.0 (1–40)	7.5 (1–64)
No. (%) with Hickman catheters	44 (70)	34 (53)

RESULTS

Patient characteristics. There were a total of 129 patients in this study. Of these, 127 were considered evaluable. The two unevaluable patients were one patient whose neutrophil count remained above 500/mm^3 and another patient whose therapy was changed on the day of randomization because of the discovery of a perirectal abscess. The characteristics of the evaluable patients according to initial randomization are shown in Table 1. None of the pretreatment variables were different on statistical grounds, but there were more patients with acute leukemia and with Hickman catheters in place in the ceftazidime arm, suggesting that more monotherapy patients were at a higher risk for infection.

Response to therapy and outcome. The two treatment strategies provided nearly identical results in all outcome categories (Tables 2 and 3). The initial clinical responses were low in both arms because of our criterion for a clinical response, i.e., defervescence within 96 h. Microbiological responses were equivalent, the single microbiological failure in the ceftazidime arm resulting from a resistant *Enterobacter cloacae* infection. The numbers of superinfections and deaths in each arm were similar. Finally, the percentages of patients surviving febrile neutropenic episodes were almost identical in both arms.

An analysis of the responses of fevers to the two approaches revealed that similar numbers of patients responded within 4 days of therapy, but another 12 (19%) in the ceftazidime arm responded to the addition of vancomycin (Tables 2 and 3). Interestingly, nine gram-positive infections required the addition of vancomycin for a response, but a total of 13 of 35 patients with gram-positive infections remained febrile even on combination therapy (Table 3). Whether this result was due to the gram-positive infections or undocumented superinfections is unclear.

Microbiological data. Two-thirds of the infecting pathogens were gram-positive bacteria divided almost equally among streptococcal species, *Staphylococcus aureus*, and *Staphylococcus epidermidis* (Table 4). All the *S. epidermidis* isolates were obtained from blood cultures. Some of these *S. epidermidis* isolates may have been contaminants, but all the patients were febrile and neutropenic at the time of the positive cultures. In the absence of other standard reliable criteria for differentiating contamination from infection in this population, all patients were treated for infections. All patients with blood isolates of *S. epidermidis* had Hickman catheters in place. All *S. aureus* infections were bacteremic

TABLE 2. Evaluation of responses to therapy

Parameter	Value for the following study arm:	
	Ceftazidime	Ceftazidime + vancomycin
Total no. of patients	63	64
Clinical response to[a]:		
Initial therapy within 4 days	35 (56)	39 (61)
Added vancomycin	12 (19)	NA[b]
Microbiological cure with[c]:		
Initial regimen	17/32	20/20
Vancomycin added per protocol or clinical state[d]	14/32	NA
Superinfection with[e]:		
Initial regimen	1	5
Vancomycin added	7	NA
Death from[f]:		
Infection	2	5
Superinfection	4	1
Other causes	0	1
Total	6 (10)	7 (11)
Survival[a]	57 (90)	57 (89)

[a] Reported as number (percent) of patients.
[b] NA, Not applicable.
[c] Reported as number of patients with the indicated parameter/total number. Microbiological cure was considered separately from the clinical response of becoming afebrile.
[d] Vancomycin was added because patients were still febrile (seven cases) or because a moderately resistant gram-positive bacterium was isolated (seven cases). No blood cultures repeated prior to the addition of vancomycin were positive.
[e] Reported as number of patients.
[f] Reported as number of patients but number (percent) of patients for total.

infections or severe tissue infections (one tracheitis and one purulent finger infection, possibly blood borne). Ten of the 33 gram-positive blood stream infections were caused by isolates belonging to the genus *Streptococcus*, a relatively new occurrence in our neutropenic patient population. These isolates included viridans group streptococci, group G beta-hemolytic streptococci, and even *Streptococcus pneumoniae*. Important for the evaluation of our strategy was the fact that the numbers of gram-positive bacteria initially isolated were similar in each arm. Surprisingly, there were more gram-negative infections in the ceftazidime arm, which also had more patients with leukemia and Hickman catheters. One would have expected more gram-positive infections in this arm because of the catheters. We have no good explanation for this result. Urinary tract isolates constituted a small proportion of our isolates, and we are unsure of their significance in the absence of urinary tract leukocytes. No doubt they may have been a source of bacteremia, but none of our patients had concomitant bacteremia.

Superinfections and deaths. With regard to superinfections, there were no unusual differences between the two arms (Table 5). In contrast to our first study (12), there was no excess of gram-positive superinfections in the patients receiving ceftazidime alone as initial therapy. Two occurrences are, however, of note; one patient died from a ceftazidime-susceptible *Pseudomonas aeruginosa* superinfection, and one died from *Escherichia coli* bacteremia caused by a strain resistant to ceftazidime (MIC, >64 μg/ml). (See the Discussion for more details). Deaths with fever of unknown etiology were categorized as infectious deaths, although no organisms were isolated.

TABLE 3. Duration of fever by regimen

Patients	Duration of fever, in days, for the following study arm (no. of patients)[a]:	
	Ceftazidime (63)	Ceftazidime + vancomycin (64)
All		
Responding to initial regimen	2.6 ± 1.8 (35)	2.2 ± 1.2 (39)
Responding to added vancomycin	6.3 ± 1.0 (12)	NA
With prolonged fevers with ceftazidime plus vancomycin[b]	12.8 ± 2.8 (16)	11.5 ± 5.2 (25)
With gram-positive infections		
Responding to initial regimen	2.8 ± 1.8 (7)	3.0 ± 2.5 (8)
Responding to added vancomycin	4.1 ± 1.8 (7)	NA
With prolonged fevers with ceftazidime plus vancomycin[b]	11.0 ± 3.3 (5)	10.2 ± 1.8 (8)

[a] Neither the duration of fever nor the number of patients in any category was significantly different between the two arms. NA, not applicable.
[b] Fever lasting >7 days while patient was on both drugs.

Features of the true monotherapy group. Twenty-one of 63 patients in the ceftazidime arm actually received true monotherapy throughout the period of neutropenia because they defervesced and did not require modification of their antibiotic therapy. These patients had lower mean and median times of neutropenia (7 and 4 days, respectively) than the whole population; nevertheless, 38% were leukemic. The survival rate among these patients was 95%, with a single superinfection and death caused by *Candida albicans*.

Antibiotic additions. Vancomycin was required in two-thirds of the cases randomized to receive monotherapy.

TABLE 4. Etiology of microbiologically documented infections

Site (no. of strains)	Organism (no. of strains) isolated in the following study arm:	
	Ceftazidime	Ceftazidime + vancomycin
Blood and/or catheter (46)[a]	Gram negative (11) *E. coli* (3) *P. aeruginosa* (3) *Klebsiella* or *Enterobacter* sp. (5)	Gram negative (2) *Haemophilus influenzae* (1) *P. aeruginosa* (1)
	Gram positive (18) *S. aureus* (6) *S. epidermidis* (5) *Streptococcus* sp. (7)	Gram positive (15) *S. aureus* (5) *S. epidermidis* (6) *Streptococcus* sp. (3) Group JK diptheroid (1)
Urine (6)	*E. coli* (2) *Enterococcus* sp. (1)	*E. coli* (1) *Proteus mirabilis* (1) *Enterococcus* sp. (1)

[a] Totals: gram negative, 13; gram positive, 33. One *S. aureus* strain was isolated only from a catheter.

TABLE 5. Superinfections and overall deaths

Study arm	Organism or condition (no. of strains) involved in:	
	Superinfections	Deaths
Ceftazidime	*Clostridium difficile* (2)	Resistant *E. coli* (1)[a]
	E. coli bacteremia (resistant) (1)	Pneumonia of unknown etiology (1)
	S. aureus bacteremia (1)[b]	*Candida* sepsis (2)[a]
	S. epidermidis bacteremia (1)	Febrile deaths (2)
	C. albicans (2)	
	Candida tropicalis (1)	
Ceftazidime plus vancomycin	*C. difficile* (2)	Susceptible *P. aeruginosa* (1)[a]
	P. aeruginosa bacteremia (1)	Febrile deaths (5)
	Pneumonia of unknown etiology (1)	Brain hemorrhage (1)
	Aspergillus sinusitis (1)	

[a] Deaths resulting from microbiologically documented superinfections.
[b] Hickman catheter site infection while patient was on vancomycin.

Therefore, one-third of patients did not receive vancomycin at all, and the rest received a mean of 4 days less than patients in the combination therapy arm (Table 6). In the entire study, only 13 patients (10%) required the addition of an aminoglycoside, mostly on an empiric basis for fever and worsening clinical condition late in the course of neutropenia. Two of these patients died, one from *P. aeruginosa* bacteremia and the other with fever of unknown etiology.

Toxicity. One of the criticisms of combination therapy is the increased risk of drug toxicity. The delay in the addition of vancomycin resulted in statistically fewer toxic reactions in the monotherapy arm (rashes and increased creatinine levels: 6 of 63 in the ceftazidime arm versus 19 of 64 in the ceftazidime-vancomycin arm; $P = 0.02$). However, all patients who suffered mild nephotoxicity (increase in creatinine levels by 50% to >2 mg/liter) were also receiving amphotericin B.

TABLE 6. Antibiotic modifications

Parameter	Value for the following study arm:	
	Ceftazidime (63 patients)	Ceftazidime + vancomycin (64 patients)
Vancomycin added for the following indication[a]	40 (63)	NA
Protocol (new fevers)[b]	21	
Clinical (persistent fevers)[b]	12	
Microbiological[b]	7	
Days of vancomycin, mean ± SD	8 ± 9	12 ± 11
Amphotericin B added[a]	25 (40)	26 (41)
Other antibiotics added[a]	12 (19)	16 (25)
Aminoglycosides	7 (11)	6 (9)
Others	5 (8)	10 (16)

[a] Reported as number (percent) of patients. NA, not applicable.
[b] Reported as number of patients.

DISCUSSION

The antibiotic therapy of febrile episodes in neutropenic cancer patients has been by necessity empiric and broad spectrum with combinations of drugs that provided high serum bactericidal activity against gram-negative pathogens (15, 19). However, the development of newer cephalosporins with higher activity against these pathogens and improved β-lactamase stability has heralded a new approach to this problem. Instead of an initial shotgun approach with two or three drugs, attempts have been made to use single drugs active against the most important pathogens and then to add carefully other agents as needed (11, 19). This approach would certainly work under certain conditions, as long as (i) the agent is active against the majority of the initial infecting microorganisms and (ii) any delay in therapeutic modification does not result in excess mortality from relatively resistant bacteria. A decade ago, aerobic gram-negative bacteria constituted the majority of initial infecting organisms; however, this spectrum has gradually changed, with gram-positive bacteria now playing a significant role. The ideal monotherapy candidate should therefore have enough activity against gram-positive bacteria to forestall excess mortality if modification is required. In a retrospective analysis, Rubin et al. (13) concluded that the addition of vancomycin could be delayed after initial ceftazidime therapy until clinically indicated. To our knowledge, this trial is the first designed to test such a strategy in a prospective, randomized fashion with specific criteria for the addition of vancomycin and confirms the soundness of this basic approach to the management of febrile episodes in neutropenic cancer patients. The concrete results of our trial were as follows: (i) there was no excess mortality with this approach; (ii) there was no excess of gram-positive superinfections; and (iii) less vancomycin was used (55% less), resulting in some cost savings.

To our knowledge, an identical prospective study has not been published, but two very large studies with somewhat different designs have come to similar conclusions. Pizzo et al. (11) came to these conclusions in analyzing the responses of patients who received monotherapy modified with the addition of other agents. The second very large study came to the same conclusions, but it appeared that vancomycin was frequently added to the non-vancomycin arm on clinical grounds (17). However, the authors claimed that the proportion of patients remaining febrile in each arm was the same even before the addition of vancomycin. Despite the fact that this was a large prospective study dealing with documented gram-positive infections, it did not provide and test criteria for the addition of vancomycin. In addition, the authors had no way of circumventing the fact that ceftazidime plus amikacin may be synergistic for gram-positive bacteria and vancomycin may not be needed with this combination, unless there is a high incidence of methicillin resistance.

The latter study (17) did, however, point out a problem encountered when gram-positive bacteremia is diagnosed—the tendency for physicians caring for such patients to add a drug more active against gram-positive bacteria, thus making evaluation difficult. This tendency was also encountered in our institutions, but not to a great degree. Patients in the ceftazidime arm received vancomycin for about 4 days less than those in the combination arm (Table 6). In fact, one-third of the patients with documented gram-positive infections did not receive this agent. The other two-thirds received it primarily because the isolates of *S. epidermidis* and

S. aureus encountered in this arm were moderately susceptible or because the fever appeared to be prolonged. Not adding vancomycin when a fever continues runs the risk of allowing a superinfection or breakthrough bacteremia. While the data from our prospective study examining the addition of vancomycin support a "stepped" approach, the other side of the coin, "front loading" with vancomycin, has been advocated for good reason. We and others have seen fatal gram-positive breakthrough bacteremia (6, 12, 16) and failure with gram-positive infections (3). More recently, fulminant alpha-hemolytic streptococcal infections have been seen in certain patients (8). However, this latter point requires more study, since such streptococci are not generally resistant to initial β-lactam therapy, and it is not certain that vancomycin would prevent such fulminant infections. All of our alpha-hemolytic streptococci were ceftazidime susceptible.

This study is noteworthy for two other important reasons. We are witnessing a profound shift in the initial infecting pathogens in our population of patients. Thirty-three of 46 pathogens isolated from the serious infections were gram-positive bacteria. It was particularly puzzling that 10 of the 33 were streptococcal species and could not be explained by the use of Hickman catheters. This shift also appears to be occurring in other institutions (8, 16, 17).

The second feature of our study which deserves comment is the need for concomitant aminoglycoside therapy. In this study, taking a carefully considered approach to the addition of aminoglycosides (for a resistant gram-negative infection or clinical deterioration late in the course of neutropenia, i.e., >2 weeks), aminoglycoside therapy was used in only 10% of patients. Among the 12 initial gram-negative bacteremias, only one resistant *E. cloacae* isolate required an aminoglycoside. It is possible that the two superinfections and deaths caused by gram-negative bacteria (a resistant *E. coli* isolate and a susceptible *P. aeruginosa* isolate) might have been prevented by the concomitant use of aminoglycosides, but this possibility is not certain. The EORTC advocates the use of an aminoglycoside with ceftazidime (18), but with the falling incidence of gram-negative bacteremia and the low rate of isolation of ceftazidime-resistant gram-negative organisms, the cost/benefit and toxicity/benefit ratios need to be assessed in each institution before this recommendation is uniformly accepted. In fact, a meta-analysis of the data on ceftazidime monotherapy supports the monotherapy approach (14). Perhaps in institutions with a high incidence of resistant gram-negative bacteria, this approach would be the desired one.

While the monotherapy strategy appears to have worked well in our population, the use of any one agent repeatedly for long periods of time may ultimately limit the usefulness of that agent. The patient with the resistant *E. coli* superinfection had received three prior courses of ceftazidime therapy. The strain that was isolated has been characterized and appears similar to the TEM-4 and TEM-6 plasmid-bearing strains recently described (10), with an isoelectric point of 5.8. The resistant *E. cloacae* isolate also represents another potential problem. We have encountered this problem previously and continue to see it in neutropenic patients who have received prior courses of ceftazidime for fever and neutropenia (5).

Thus, while we are enthusiastic about the monotherapy strategy, there is a risk that resistant gram-negative superinfections will pose an increasing threat to patients receiving multiple courses of the same agents, as can occur with leukemic patients. It is not at all clear that aminoglycosides will prevent this problem. At the present time, our strategy for the use of ceftazidime monotherapy consists of ceftazidime as the sole initial drug and the addition of vancomycin with the isolation of gram-positive bacteria relatively resistant to ceftazidime (MIC, ≥8 μg/ml or for new or persistent fevers after 4 days of monotherapy. An aminoglycoside is added when a resistant gram-negative organism is isolated initially or anytime during ceftazidime therapy. Clinical deterioration in patients with prolonged neutropenia, which may herald a superinfection, is also managed by the empiric addition of an aminoglycoside.

ACKNOWLEDGMENTS

We thank Leanne Forsyth for preparation of the manuscript and David Shlaes of Case Western Reserve University for characterizing the *E. coli* isolate.

REFERENCES

1. **Anaissie, E. J., V. Fainstein, G. P. Bodey, K. Rolston, L. Elting, H. Kantarjian, F. Cabanillas, and K. B. McCredie.** 1988. Randomized trial of beta-lactam regimens in febrile neutropenic cancer patients. Am. J. Med. **84:**581–589.
2. **Del Favero, A., F. Menichetti, R. Guerciolini, G. Bucaneve, F. Baldelli, F. Aversa, A. Terenzi, S. Davis, and S. Pauluzzi.** 1987. Prospective randomized clinical trial of teicoplanin for empiric combined antibiotic therapy in febrile, granulocytopenic acute leukemia patients. Antimicrob. Agents Chemother. **31:**1126–1129.
3. **Fainstein, V., G. P. Bodey, L. Elting, R. Bolivar, M. J. Keating, K. B. McCredie, and M. Valdivieso.** 1983. A randomized study of ceftazidime compared to ceftazidime and tobramycin for the treatment of infections in cancer patients. J. Antimicrob. Chemother. **12**(Suppl. A):101–110.
4. **Granowetter, L., H. Wells, and B. J. Lange.** 1988. Ceftazidime with or without vancomycin versus cephalothin, carbenicillin and gentamicin as initial therapy of the febrile neutropenic pediatric cancer patient. Pediatr. Infect. Dis. J. **7:**165–170.
5. **Johnson, M. P., and R. Ramphal.** 1990. β-Lactam resistant *Enterobacter* bacteremia in febrile neutropenic patients receiving monotherapy. J. Infect. Dis. **162:**981–983.
6. **Karp, J. E., J. D. Dick, C. Angelopulos, P. Charache, L. Green, P. J. Burke, and R. Saral.** 1986. Empiric use of vancomycin during prolonged treatment-induced granulocytopenia. Am. J. Med. **81:**237–242.
7. **Kramer, B. S., R. Ramphal, and K. H. Rand.** 1986. Randomized comparison between two ceftazidime-containing regimens and cephalothin-gentamicin-carbenicillin in febrile granulocytopenic cancer patients. Antimicrob. Agents Chemother. **30:**64–68.
8. **McWhinney, P. H. M., S. H. Gillespie, C. C. Kibbler, A. V. Hoffbrand, and H. G. Prentice.** 1991. Streptococcus mitis and ARDS in neutropenic patients. Lancet **337:**429.
9. **Novakova, I., J. P. Donnelly, and B. D. Pauw.** 1991. Ceftazidime as monotherapy or combined with teicoplanin for initial empiric treatment of presumed bacteremia in febrile granulocytopenic patients. Antimicrob. Agents Chemother. **35:**672–678.
10. **Philippon, A., R. Labia, and G. Jacoby.** 1989. Extended-spectrum β-lactamases. Antimicrob. Agents Chemother. **33:**1131–1136.
11. **Pizzo, P. A., J. W. Hathorn, J. Hiemenz, M. Browne, J. Commess, D. Cotton, J. Gress, D. Longo, D. Marshall, J. McKnight, M. Rubin, J. Skelton, M. Thaler, and R. Wesley.** 1986. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. N. Engl. J. Med. **315:**552–558.
12. **Ramphal, R., B. S. Kramer, K. H. Rand, R. S. Weiner, and J. W. Shands, Jr.** 1983. Early results of a comparative trial of ceftazidime versus cephalothin, carbenicillin and gentamicin in the treatment of febrile granulocytopenic patients. J. Antimicrob. Chemother. **12**(Suppl. A):81–89.
13. **Rubin, M., J. W. Hathorn, D. Marshall, J. Gress, S. M. Steinberg, and P. A. Pizzo.** 1988. Gram positive infections and

the use of vancomycin in episodes of fever and neutropenia. Ann. Intern. Med. **18:**30–35.
14. **Sanders, J. W., N. R. Powe, and R. D. Moore.** 1991. Ceftazidime monotherapy for empiric treatment of febrile neutropenic patients: a metaanalysis. J. Infect. Dis. **164:**907–916.
15. **Sculier, J. P., and J. Klastersky.** 1984. Significance of serum bactericidal activity in gram-negative bacillary bacteremia in patients with or without granulocytopenia. Am. J. Med. **76:**429–435.
16. **Shenep, J., W. T. Hughes, P. I. Robertson, K. R. Blankenship, D. K. Baker, Jr., W. H. Meyer, F. Gigliotti, J. W. Sixbey, V. M. Santana, S. Feldman, and L. Lott.** 1988. Vancomycin, ticarcillin and amikacin compared with ticarcillin-clavulanate and amikacin in the empirical treatment of febrile neutropenic patients with cancer. N. Engl. J. Med. **319:**1053–1058.
17. **The EORTC and National Cancer Institute of Canada.** 1991. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic cancer patients. J. Infect. Dis. **163:**951–958.
18. **The EORTC International Antimicrobial Therapy Cooperative Group.** 1987. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. N. Engl. J. Med. **317:**1692–1698.
19. **The Infectious Diseases Society of America.** 1990. Guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. J. Infect. Dis. **161:**381–396.
20. **Viscoli, C., C. Moroni, L. Boni, P. Bruzzi, A. Comelli, G. Dini, A. Fabbri, V. Secondo, and A. Terragna.** 1991. Ceftazidime plus amikacin versus ceftazidime plus vancomycin as empiric therapy in febrile neutropenic children with cancer. Rev. Infect. Dis. **13:**397–404.