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A Randomized Prospective Study of Ceftazidime Versus Ceftazidime Plus Flucloxacillin in the Empiric Treatment of Febrile Episodes in Severely Neutropenic Patients

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In a prospective, randomized study, ceftazidime monotherapy was compared with a combination of ceftazidime and flucloxacillin in 100 febrile neutropenic patients. Thirty-four bacteriologically documented infections, of which 26 were bacteremias, in 51 patients were treated with ceftazidime alone. Thirty-four bacteriologically proven infections, of which 29 were bacteremias, in 49 patients were treated with a combination of ceftazidime and flucloxacillin. The clinical response rate for ceftazidime monotherapy was 80%; the bacteriological cure rate was 90%. Efficacy against gram-negative pathogens appeared to be excellent, achieving a 100% cure rate. The clinical response and bacteriological cure rates for the combination were 76 and 86%, respectively. Three superinfections were registered in the ceftazidime group, and four, involving six pathogens, were registered in the combination group. Other side effects of ceftazidime were minimal. It is concluded that ceftazidime is an effective drug for the empiric treatment of febrile neutropenic patients. It offers the opportunity to avoid the aminoglycosides in first-line treatment. It may be appropriate to combine ceftazidime with cephalotin or vancomycin or to modify therapy if resistant gram-positive strains are encountered.

Empiric antibiotic therapy has become standard practice for the initial management of febrile episodes in neutropenic patients. However, in most centers treating cancer patients, infection remains the leading cause of morbidity and mortality. Although early death due to inadequately treated bacterial infection has been largely overcome with early empiric antibiotic therapy, new problems have emerged. Aminoglycosides, extremely effective in vitro against most pathogens isolated from neutropenic patients, show a narrow margin between effective and toxic doses. Concern over possible nephrotoxicity and ototoxicity may lead to underdosing. Furthermore, other potentially nephrotoxic drugs such as cisplatinum and cyclosporin A are increasingly used in these patients.

The availability of ceftazidime, a new cephalosporin antibiotic, offers, in view of its spectrum of activity (9), the option to omit the aminoglycosides, along with their adverse effects, in first-line treatment. The efficacy of ceftazidime alone in the empiric treatment of febrile neutropenic patients has already been established (5, 11). Because ceftazidime has only moderate in vitro activity against staphylococci, we conducted a prospective randomized study comparing ceftazidime alone with a combination of ceftazidime plus flucloxacillin. The protocol was agreed upon by the local ethical committee before the study.

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MATERIALS AND METHODS

This study was performed at the Division of Hematology, University Hospital St. Radboud, Nijmegen, The Netherlands.

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Clinically septicemic patients over 15 years of age with an absolute granulocyte count of $<1{,}000/mm^3$ and two consecutive temperature readings taken 4 h apart of 38.5°C or greater in association with chills and in the absence of an obvious noninfectious cause of fever were eligible for the study. Patients with a history of allergy to one of the drugs used or patients who had been treated with other systemic antibacterial agents, except for oral administration of co-trimoxazole, in the previous 72 h, were excluded from the study. All patients were nursed in reverse isolation and received prophylactically, before the occurrence of fever, selective gut decontamination, which consisted of oral therapy with 960 mg of co-trimoxazole every 8 h, 100 mg of colistin every 6 h, and 100 mg of ketoconazole every 6 h. In the event of allergy, co-trimoxazole was replaced by 250 mg of neomycin every 6 h (five cases), and in case of ketoconazole hypersensitivity, 400 mg of amphotericin B every 6 h was substituted (six cases). Pretreatment evaluation included complete history, physical examination, and cultures from the blood (three cultures from three different sites on three separate occasions), urine, mouth, throat, ear, axillae, groin, perineum, and any clinically suspicious lesion (e.g., the sputum). The feces were examined for *Salmonella*, *Shigella*, and *Campylobacter* organisms, *Staphylococcus aureus*, and yeasts and for the quantitative presence of members of the family of *Enterobacteriaceae*. A midstream urine was analyzed for protein, leukocytes, erythrocytes, microorganisms, and casts.

A complete blood count, thrombocyte count, leukocyte count, and differential were performed, and serum creatinine, bilirubin, glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, alkaline phosphatase, and protein electrophoresis were determinated.

The institution of antibiotic therapy was not delayed for these procedures to be completed. After informed consent

TABLE 1. Clinical data on the treated patients

Parameter	Drug(s)	
	Ceftazidime	Ceftazidime and flucloxacillin
No. of patients (men/women)	51 (36/16)	49 (30/19)
Mean age (yr; range)	32.5 (16–75)	36.2 (16–68)
Mean weight ± standard deviation (kg; range)	66.4 ± 12.1 (42.1–98.8)	66.0 ± 11.5 (40.5–92.2)
Mean dose of ceftazidime (mg/kg of body weight; range)	92.6 ± 17.6 (60.7–142.5)	92.8 ± 18.1 (65.1[a]–148.1)
No. of patients with bacteriologically proven infections	36	34
No. of patients with two unique infection sites	1	0
No. of patients with misdiagnosis (i.e., fungal or viral infection)	3	2
No. of patients with underlying disease		
Acute leukemia	39	38
Chronic leukemia in blastic transformation	7	5
Malignant lymphoma	3	1
Aplastic anemia	1	
Solid tumor	1	5
No. of patients with additional complications (bone marrow transplantation)	14	6
No. (%) of patients with granulocyte count at start of treatment:		
$<250/mm^3$	31 (61)	31 (63)
$250–500/mm^3$	9 (18)	11 (23)
$501–1,000/mm^3$	11 (21)	7 (14)

[a] Excluding one patient with impaired renal function.

was obtained, the patients were randomly allocated to receive either ceftazidime (2 g intravenously every 8 h) or a combination of ceftazidime (2 g intravenously every 8 h) and flucloxacillin (2 g intravenously every 6 h). Ceftazidime was administered as a 30-min infusion, and flucloxacillin was administered as a 1-min bolus injection. When systemic therapy was started, selective gut decontamination was terminated, except for the antifungal compound. Hematological, biochemical, and clinical studies and urine analysis were repeated three times weekly. Blood cultures were obtained daily while the patient remained febrile, and the other cultures, as mentioned above, were repeated twice weekly. Patients were treated for at least 72 h unless adverse reactions or isolation of a pathogen resistant to the antibiotic(s) administered, in the presence of a deteriorating clinical status, urged a change in therapy. The empiric therapy was evaluated at 72 h and modified only if the patient did not respond. All cases in which therapy was stopped or modified before 72 h were classed as treatment failures. All deaths were classed as failures, although in some cases infection was not the primary cause of death.

Therapy was generally continued until the patient was 4 days free of the symptoms of infection. During the first 72 h, no granulocyte transfusions were added. Antibiotic responses were clinically classified as follows. (i) Success. Clinical findings subsided in a reasonable period of time with no evidence of infection or recrudescence of fever at the time the drugs were discontinued or during follow-up. (ii) Success with modification. Resolution of the infectious symptoms only after modification of the treatment regimens. (iii) Failure. No clinical response to therapy or treatment modification, or death within 72 h. (iv) Unassessable. Proven fungal or viral infections, or protocol violation. Microbiological responses were defined for each regimen as (i) eradication of the original causative organism, (ii) failure (cultures remained positive), (iii) unassessable (as in the clinical definition, supplemented by lack of positive cultures within 72 h before starting treatment). Superinfection or colonization was indicated as any infection by an organism not recognized as the initial causative organism; in colonization, the patient did not require further treatment. The chi-square test was used to perform the statistical analysis of the overall clinical and bacteriological results, and Fisher's exact test was used to evaluate the incidence of rashes.

RESULTS

One hundred patients were included in the study. Infections were predominantly cases of septicemia and infections of the respiratory tract, cutaneous lesions, or oral cavity. The clinical data are summarized in Table 1. Severely neutropenic patients, males and females, and underlying diseases were evenly distributed between both study groups, which were also balanced with respect to age and weight. Fifty-one patients, one of whom had a urinary tract infection and a chest infection, were treated by ceftazidime alone; 36 patients (involving 44 organisms) had bacteriologically documented infections. Forty-nine patients, of whom 34 had a bacteriologically proven infection, were treated by a combination of ceftazidime and flucloxacillin. Three infections in the ceftazidime group and two in the ceftazidime plus flucloxacillin group were considered clinically unassessable for response, although all were evaluable for safety and tolerance. The reasons why some cases were not assessed were as follows. Two patients in the ceftazidime group had a fungal infection due to *Candida albicans*, and one had an infection with cytomegalovirus (CMV). In the ceftazidime plus flucloxacillin group, two patients were clinically unassessable. One had elevated antibody titers to CMV as the only documented evidence of infection, and one had a *C. albicans* infection.

The results of treatment are shown in Table 2, and details are shown in Tables 3 and 4. Ceftazidime as empiric monotherapy was successful in 80% of the cases with a return of temperature and clinical condition to normal, and a further 14% responded to additional antibiotics or antifungal agents. Thirty-seven of 49 (76%) infections treated with ceftazidime plus flucloxacillin responded clinically, and a further 12% responded after the addition of antibacterial or

TABLE 2. Overall results of therapy

Parameter	Drug(s)	
	Ceftazidime	Ceftazidime + flucloxacillin
No. of patients	51	49
Days of therapy with ceftazidime (mean ± standard deviation; range)	8.9 ± 4.3 (0.25–26)	8.8 ± 4.1[a] (1–22)
Clinical outcome (no. [%] of patients)		
Cure-empiric therapy	41 (80)	37 (76)
Cure-modified therapy	4 (8)	6 (12)
Failure	3 (6)	4 (8)
Unassessable (viral and fungal infections)	3 (6)	2 (4)
Bacteriological outcome (no. [%] of patients)		
Eradication	37 (90)	30 (86)
Failure	4 (10)	5 (14)
Granulocyte count[b] (% of patients) at time of response:		
<250/mm^3	65	77
250–500/mm^3	17	9
501–1,000/mm^3	16	11
>1,000/mm^3	2	3

[a] Eleven patients had shortened courses of flucloxacillin; the mean duration of treatment ± the standard deviation was 7.5 ± 3.0 days, with a range of 2 to 16 days.
[b] For successfully treated patients.

antifungal agents. In 37 of 41 (90%) cases, the causative organisms were eradicated by ceftazidime alone. A bacteriological clearance was achieved in 30 of 35 (86%) assessable initial isolates by ceftazidime plus flucloxacillin. One patient with positive blood cultures of *Clostridium perfringens* and *Klebsiella pneumoniae* and high antibody titers against CMV was treated only for 3 days, refusing all further treatment. The failures included one patient admitted in septic shock with *Streptococcus pneumoniae* isolated from the blood who died after only one dose of ceftazidime. Details on those patients who did not have a successful outcome with initial empiric therapy are given in Table 4. At the time of response, the majority of the successfully treated patients were still profoundly neutropenic: 30 (65%) had fewer than 250 granulocytes per mm^3 in the ceftazidime group, compared with 27 (77%) in the ceftazidime plus flucloxacillin group. In 6 (12%) infections in the ceftazidime group for which a posttreatment neutrophil count was performed and in 9 of 38 (24%) infections in the ceftazidime and flucloxacillin group, successful treatments were associated with an increase in the granulocyte count of 250/mm^3 or more. In the ceftazidime group, 36 of the 51 patients had bacteriologically documented infections; 30 responded to monotherapy, 3 responded to modified therapy, and 3 failed to respond. Of the 15 bacteriologically undocumented infections, 3 were ultimately shown to be of viral or fungal origin and received appropriate, successful therapy; 11 were cured with ceftazidime alone, and 1 failed to respond and the patient died after the addition of cephalotin and vancomycin for a staphylococcal superinfection. Of the 49 patients treated with ceftazidime plus flucloxacillin, 34 had bacteriologically documented infections; 30 responded overall, 25 to the initial therapy and 5 to modified therapy; and 4 failed to respond. Of the 15 bacteriologically undocumented patients receiving ceftazidime plus flucloxacillin, 2 had viral or fungal infections and the remainder responded, including 1 who responded after modification of therapy. If successful empiric therapy is defined as a clinical cure of a surviving patient without the need for further antibiotic therapy, this was represented by 41/51 in the ceftazidime group and 37/49 in the ceftazidime and flucloxacillin group.

The bacteriological results, based on positive cultures obtained before treatment, are shown in Table 5. There was a slightly better response of staphylococci to the combination (8 of 12) than to ceftazidime alone (3 of 6), but otherwise no difference between the treatment groups was observed.

None of the 50 gram-negative infections in either group failed to respond, except in the case of gram-positive superinfections. During ceftazidime treatment, four superinfections were registered: two *Staphylococccus epidermidis*, one *Streptococcus viridans*, and one *Bacillus* species, all caused by organisms resistant to ceftazidime. In three patients who received ceftazidime plus flucloxacillin, superinfections with five organisms resistant to both antibiotics occurred, due to enterococci, *Bacteroides* sp., *S. epidermidis*, *C. albicans*, and *Bacillus* sp. One patient also became colonized with *C. albicans*.

Seven patients showed a flucloxacillin-related erythroderma, causing early termination of administration of the drug. No allergic reaction to ceftazidime was seen. In both groups, two patients showed temporary increases of glutamic-oxaloacetic and glutamic-pyruvic transaminases, which could have been attributable to the ceftazidime. None of the patients had any sign of nephrotoxicity as measured by serum creatinine levels or of ototoxicity. No local reactions to the drugs were seen. During treatment, the numbers of organisms of the family *Enterobacteriaceae* in the ceftazidime group remained below 100/g of feces, whereas an increase above this value was noted in 80% of the patients who had been treated with the flucloxacillin-containing combination for more than 5 days.

TABLE 3. Summary of clinical results

Result	No. of patients taking the following drug(s)	
	Ceftazidime	Ceftazidime and flucloxacillin
Empiric success		
Blood culture positive	21	21
Other than blood culture positive	9	4
No positive cultures	11	12
Success with modification		
Blood culture positive	2	5
Other than blood culture positive	1	0
No positive culture	1	1
Failure		
Blood culture positive	3	3
Other than blood culture positive	0	1
No positive culture	0	0
Nonbacterial and empiric failure	3[a]	2[b]

[a] One CMV; two fungal.
[b] One CMV; one fever related to malignancy.

TABLE 4. Success after modification and failure of therapy

Outcome	Original isolate	Superinfection	Ceftazidime susceptibility (original/superinfection)	Rescue scheme (result)
Success after modification of ceftazidime monotherapy	*S. aureus* (blood)	Anaerobe	Resistant/resistant	Cephalotin + metronidazole
	S. epidermidis (blood)		Resistant	Cephalotin
	S. epidermidis (skin)		Resistant	Cephalotin + vancomycin
	No positive culture	*S. epidermidis*	/Resistant	Cephalotin + vancomycin
Failure of ceftazidime monotherapy	*S. pneumoniae*		Susceptible	(Patient died after one dose)
	K. pneumoniae and *Clostridium* species		Susceptible/resistant	Penicillin G (day 2; patient refused treatment; patient died)
	Escherichia coli	*S. viridans*	Susceptible/susceptible	Vancomycin + amikacin (patient died)
Success after modification of ceftazidime + flucloxacillin	*Pseudomonas aeruginosa*	*S. epidermidis* and enterococci	Susceptible/resistant/resistant	Addition of cephalotin + amikacin
	S. aureus	Enterococci	Resistant/resistant	Cephalotin + amikacin
	S. epidermidis[a]		Resistant/	Cephalotin
	S. epidermidis[a]		Resistant/	Cephalotin + amphotericin B
	S. epidermidis		Resistant/	Cephalotin + vancomycin
	No positive culture	Anaerobes	/Resistant	Penicillin G
Failure of ceftazidime + flucloxacillin	*Haemophilis influenzae* (throat)	*Bacillus* and *Candida* sp.	Susceptible/resistant/resistant	Amikacin + erythromycin + amphotericin B (patient survived)
S. viridans	*S. viridans* and *S. epidermidis*		Susceptible/intermediate	(Patient died)
	S. aureus		Susceptible	(Patient died day 4 of cerebral hemorrhage)
	E. coli		Susceptible	(*E. coli* cleared; patient died of cardiac arrest)

[a] Originally susceptible to flucloxacillin; became resistant during treatment.

DISCUSSION

The data from this study and others (5, 11) suggest that ceftazidime alone or in combination with another antibiotic may be used for the initial therapy of granulocytopenic patients with fever. Bone marrow recovery was not an important factor in the cure of patients, because only a small minority of the patients had a substantial increase of their granulocyte counts during treatment. This has become associated with good response rates in many other studies (2, 4, 7, 14).

No differences in response rate between the two study arms were found. A slight tendency to higher efficacy of the combination was observed in *S. epidermidis* and *S. aureus* infections, although there were only three and four failures, respectively. However, there was one staphylococcal superinfection in the combination group, and two strains became resistant to flucloxacillin. More superinfections emerged during treatment with flucloxacillin plus ceftazidime, which may have been caused by disturbance of the colonization resistance (13, 15) by the penicillin derivate, which occurred in 80% of the patients. Moreover, the administration of flucloxacillin had to be terminated in seven patients because of an allergic reaction. Otherwise, toxicity in this study was minimal and limited to transient elevations of serum transaminases. Absence of nephrotoxicity and ototoxicity seems the major advantage of the use of ceftazidime over the aminoglycosides, especially because another nephrotoxic and ototoxic drug, such as cyclosporin A and cisplatinum, may be given to patients in this category.

Using relatively high doses of ceftazidime during relatively short periods of time, we did not observe the induction of ceftazidime resistance in previously susceptible organisms, a concern in the use of the new extended-spectrum cephalosporins (12). Pending the results of microbiological cultures, the primary objective of empiric antibiotic therapy is to protect the patient from immediate death. Therefore, the antibiotic regimen selected must contain activity against the major pathogens (8). Ceftazidime alone fulfils these criteria, as has been demonstrated by this and previous studies (5, 11). Six patients, three in each group, died, in part due to underlying conditions; the results described, with 94% of the patients responding, compared favorably to results obtained with two- or three-drug regimens (1, 6, 11). Considering the cure rate of ceftazidime alone, it may become a cornerstone of empiric antibiotic combinations in the treatment of immunocompromised hosts. Local circumstances may influence the composition of such a combination, aiming at extending the spectrum of activity and accomplishing antibiotic synergy. This may become important, because the spectrum of infecting organisms has undergone considerable changes during the last few decades. In the 1950s and early 1960s, *S. aureus* was the most frequently cultured organism, whereas during the late 1960s and the 1970s, gram-negative bacteria became predominant (10). In some centers, however, gram-positive bacteria are again the

TABLE 5. Distribution of pathogens and results of therapy in absolute numbers[a]

Organism	Result (no. of patients) with			
	Ceftazidime		Ceftazidime + flucloxacillin	
	Success	Failure	Success	Failure
S. aureus	1	1	2	1
S. epidermidis	2	2	6	3
Streptococcus group A	4		1	
S. pneumoniae		1	1	
Streptococcus sanguis	4[b]		1	1
Streptococcus faecalis	1		1	
H. influenzae	3		2	
E. coli	6		2	
Enterobacter cloacae	2		4	
Citrobacter freundii	1			
Klebsiella oxytoca			1	
K. pneumoniae	3		2	
Proteus mirabilis	2		3	
Acinetobacter sp.	1		1	
P. aeruginosa	7[b]		3	

[a] Unassessable cases are not included (three with ceftazidime and two with ceftazidime and flucloxacillin). Overall, ceftazidime and ceftazidime and flucloxacillin had success rates of 90 and 86%, respectively.

[b] One patient in each case had the organism eliminated from the blood. However, posttreatment *S. sanguis* could still be grown from a soft tissue site and *P. aeruginosa* could be grown from the sputum in these clinically well patients.

most common pathogens, probably due to changing medical practices (3).

Of particular concern are *S. viridans* and *S. epidermidis*, especially in patients with indwelling venous catheters. In some cases, *S. epidermidis* is methicillin resistant, and such infections require treatment with vancomycin (2).

In conclusion, it may be stated that ceftazidime is an effective drug for initial empiric antibiotic therapy in febrile granulocytopenic patients, offering the possibility of avoiding the aminoglycosides and their inherent nephrotoxicity and ototoxicity. However, if a staphylococcal etiology is suspected, combination with a drug such as vancomycin is advocated.

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