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Randomized Evaluation of Ceftazidime or Ticarcillin and Tobramycin for the Treatment of Osteomyelitis Caused by Gram-Negative Bacilli

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Ceftazidime, a new cephalosporin with enhanced activity against aerobic gram-negative bacilli, was compared with tobramycin and ticarcillin in a randomized clinical trial. Efficacy and safety were evaluated in 18 patients (17 males, 1 female) with gram-negative osteomyelitis. All organisms were susceptible to the treatment antibiotics(s). There were nine patients treated with tobramycin and ticarcillin for 27 to 62 days (mean, 42 days), and nine patients were treated with 4 g of ceftazidime per day for 26 to 63 days (mean, 45 days). All nine patients receiving tobramycin and ticarcillin had the osteomyelitis arrested after the initial treatment. Follow-up was for 2 to 38 months (mean, 22 months). Of nine patients receiving ceftazidime three were initial treatment failures. Follow-up was for 13 to 31 months (mean, 21 months). A patient receiving ceftazidime had a transient rise in serum glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase. There were three treatment failures in the ceftazidime group; no failures occurred in the group receiving the combination of ticarcillin and tobramycin. A larger series would be required to detect a significant difference between the two treatment groups.

Gram-negative osteomyelitis is frequently a polymicrobic infection usually occurring after traumatic injury. Of the gram-negative organisms isolated from patients with osteomyelitis at the University of Texas Medical Branch (UTMB), *Pseudomonas aeruginosa* was the most common isolate. Treatment of this organism usually involves one of the aminoglycosides in combination with an extended-spectrum penicillin. The aminoglycosides are inactivated by low pH and decreased oxygen tensions (5, 12). Both of these conditions are commonly found in infected bone. There is also increased risk of nephrotoxicity and ototoxicity with the prolonged use of aminoglycosides. The extended-spectrum penicillins require frequent dosing and may cause sodium loading and platelet dysfunction.

Ceftazidime, a new extended-spectrum cephalosporin, may overcome some of the limitations of the extended-spectrum penicillins plus the aminoglycosides for the treatment of severe gram-negative infections such as osteomyelitis (3, 4). Ceftazidime has significant in vitro activity against numerous species of gram-negative bacteria including *P. aeruginosa* (8, 9, 11, 14). Ceftazidime may be administered every 12 h, thereby making outpatient treatment of osteomyelitis more feasible. In this study we describe the results of a randomized comparison of ceftazidime versus a combination of ticarcillin and tobramycin for the treatment of gram-negative bacterial osteomyelitis.

MATERIALS AND METHODS

Patients admitted to this study had a biopsy-proven diagnosis of osteomyelitis. The study subjects were 18 years of age or older and gave informed written consent. The female patient was not pregnant. Patients gave no history of severe renal disease (creatinine levels greater than 2.0 mg/dl), hepatic disease, or any other significant underlying disease process. No patient had a history of allergy to cephalosporins or penicillins. Most patients had received no antibiotic therapy within 3 days before receiving the study drug(s). However, if a pathogen was resistant to the antimicrobial regimen and was susceptible to the study drugs, a change was made immediately. If a patient had lesions with gram-positive aerobic organisms or if a *Bacteroides fragilis*-group anaerobe was isolated, the patients were excluded from the study. Patients were randomized sequentially to groups that received either ceftazidime at a dosage of 2 g every 12 h or both ticarcillin at a dosage of 3 g every 4 h and tobramycin at 1.5 mg/kg every 8 h. The tobramycin dosage was adjusted to maintain a peak concentration in serum of between 4 and 5 μg/ml and a trough concentration of less than 2 μg/ml. Either antibiotic regimen was given at least 4 weeks after the last major debridement surgery. All patients with long bone osteomyelitis were staged by using the Cierny-Mader classification system (1, 2) according to the anatomic type and physiologic class of the disease.

The Cierny-Mader system defines the anatomic types of osteomyelitis as types 1, medullary; 2, superficial; 3, localized; and 4, diffuse. The physiologic class of the host was classified as normal (A), systemic compromise (B^S), local compromise (B^L), and requiring suppressive or no treatment which was characterized by minimal disability in which the treatment would be worse than the disease (C); the host in this physiologic class would not be a surgical candidate.

A clarification of local and systemic factors that adversely affected the host response follows. Indications of systemic compromise of the host (B^S) were malnutrition, immune deficiency, chronic hypoxia, malignancy, diabetes mellitus, extremes of age, and renal or liver failure or both. Indications of local compromise of the host (B^L) were chronic lymphoedema, venous stasis, major vessel compromise, arteritis, extensive scarring, and radiation fibrosis.

By using this classification system the clinical stage of a patient could be determined by combining the type and class of the osteomyelitis that was observed. For example, stage

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TABLE 1. Results of treatment with ceftazidime in nine patients with osteomyelitis

Patient age (yr)	Site/stage[a]	Organism isolated	MICs and MBCs (μg/ml) of indicated drug in Mueller-Hinton broth			Bactericidal titer peak/trough of drug in serum	Duration of follow-up (mo)	Recurrence/isolated organism(s)
			Tobramycin	Ceftazidime	Ticarcillin			
34	Femoral condyle/2A	*Alcaligenes faecalis*	1.56/3.13	3.13/3.13	0.39/100.00	1:32/1:2	13	No
41	Tibia/3A	*P. aeruginosa* *Peptococcus magnus*	0.78/12.50	0.78/6.25	50.00/50.00	1:2/G[b]	18	No/*P. aeruginosa* from Papineau site
21	Tibia/3A	*P. aeruginosa*	0.39/6.25	1.56/25.00	25.00/50.00	1:2/G	26	No/*P. aeruginosa* from pin tract
43	Tibia/3A	*P. aeruginosa* *Serratia marcescens*	0.78/12.50 100.00/100.00	0.39/1.56 0.39/0.39	25.00/25.00 100.00/100.00	fs2.5G:G 1:128/1:4	14	No
32	Tibia/3B^{L}	*Proteus mirabilis*	1.56/6.25	0.05/0.19	0.78/6.25	1:16/1:4	27	Yes/*Proteus mirabilis*, *E. coli*, *Enterococcus* sp.
31	Femur/3B^{L}	*Serratia marcescens*	0.10/0.10	0.78/12.50	3.13/6.25	1:64/1:8	31	No
25	Tibia/4B^{L}	*Pseudomonas maltophilia* *E. cloacae*	0.78/12.50 0.78/3.13	1.56/3.13 3.13/3.13	100.00/100.00 6.25/6.25	1:2/G 1:2/1:2	14	Yes/*Enterococcus* sp., *E. cloacae*, *Staphylococcus aureus*
46	Hip prosthesis/4B^{L}	*E. cloacae*	0.78/1.56	1.56/3.13	3.13/12.50	1:64/1:2	18	Yes/*E. cloacae*
20	Tibia/4B^{L}	*E. cloacae*	0.78/3.13	0.78/3.13	3.13/6.25	1:32/1:2	24	No

[a] See Materials and Methods for a description of the classification system used for determining stage of disease.
[b] G, Growth in concentrated serum.

4B^{S} osteomyelitis is characterized by a diffuse lesion in a systemically compromised host.

The terms acute and chronic osteomyelitis were not used in this staging system. However, the presence of infected necrotic bone within a compromised soft tissue envelope which required surgical debridement was synonymous with chronic osteomyelitis.

A diagnosis of osteomyelitis was made on the basis of clinical and radiographic evidence of infection. Isolation of a causative pathogen(s) was obtained from a surgical biopsy of the infected bone before the initiation of therapy. Follow-up bone cultures were also obtained at debridement surgery, usually 7 to 10 days after the initiation of therapy. Protocol debridement was performed every 3 to 5 days until all necrotic bone was removed. The bone specimens were cultured aerobically and anaerobically. MICs and MBCs of the drugs for aerobic organisms were determined by standard tube dilution techniques in Mueller-Hinton broth.

Peak and trough bactericidal titers were determined by standard techniques on most aerobic isolates during antibiotic therapy (7). For ceftazidime, peak serum titers were obtained 30 min after intravenous infusion, and trough titers were obtained immediately before the next dose of antibiotic. For patients receiving ticarcillin and tobramycin, peak serum concentrations were obtained 30 min after sequential administration of these antibiotics, and the trough level was obtained immediately before the next dosage of tobramycin.

A physical examination was performed on each patient at the beginning and at the completion of therapy. A complete blood count, sedimentation rate (Wintrobe), blood chemistry profile, and urinalysis were done before the initiation of therapy, at weekly intervals during therapy, and on follow-up examinations. Weekly serum tobramycin concentrations were determined for patients receiving tobramycin.

A clinical response was considered satisfactory osteomyelitis arrested if there was no evidence of infection at the completion of therapy, on follow-up examinations, or both. Treatment failures were defined by the presence of pain, swelling, erythema, or draining sinus tracts. Follow-up bone cultures were not obtained at the completion of therapy in the group with a satisfactory result because bone aspiration could not be justified after healing had occurred. No oral antibiotics were prescribed after therapy.

Isolates of *P. aeruginosa* from all osteomyelitis patients treated at UTMB during the 18 months of this study were stored at −70°C in sterile defibrinated sheep's blood. After completion of the study, the MICs and MBCs of ceftazidime and tobramycin for these organisms were determined.

RESULTS

A total of 18 patients was evaluated. All patients had infected necrotic bone within a compromised soft tissue envelope which required debridement surgery. A group of nine patients (eight males, one female) received ceftazidime administered intravenously at a dosage of 2 g every 12 h. Duration of therapy ranged between 26 and 63 days (mean, 45 days). The mean age of the treatment group was 32.5 years.

There were 12 organisms isolated from the nine patients (Table 1). *P. aeruginosa* and *E. cloacae* were the most common organisms isolated (three patients each). A single organism was isolated in six patients. The three remaining patients had two organisms isolated. Osteomyelitis was considered to be arrested at the end of therapy and on follow-up examination in six of the nine patients. Follow-up ranged between 13 and 31 months (mean, 21 months).

There were three patients who were considered ceftazidime treatment failures. A 32-year-old male presented to UTMB with 3B^{L} osteomyelitis of the midtibia dating from plate fixation of an open tibial fracture 5 years earlier. *Proteus mirabilis* grew on bone biopsy cultures. The patient underwent debridement surgery, plate removal, and open cancellous bone grafting (Papineau graft). The patient received a 42-day course of parenteral ceftazidime treatment, and 18 months after the completion of therapy the drainage recurred. Bone cultures at the time of debridement for the

TABLE 2. Results of treatment with ticarcillin and tobramycin in nine patients with osteomyelitis

Patient age (yr)	Site/stage[a]	Organism isolated	MICs and MBCs (μg/ml) of indicated drug in Mueller-Hinton broth			Bactericidal titer (peak/trough) of tobramycin and ticarcillin in serum	Duration of follow-up (mo)	Recurrence
			Tobramycin	Ceftazidime	Ticarcillin			
32	L2-3 spine/1A	*P. aeruginosa*	0.39/1.56	1.56/50.00	12.50/50.00	1:4/1:2	12	No
21	Radius, ulna/2A	*Proteus vulgaris*	3.13/6.25	0.39/0.78	12.50/25.00	1:16/G[b]	16	No
43	Femur/3A	*Proteus* sp.	1.56/6.25	0.19/0.39	0.78/3.13	1:32/1:2	18	No
35	Tibia/3A	*P. aeruginosa*	0.10/0.14	0.10/0.29	25.00/50.00	1:4/1:2	24	No
67	Sternum/$3B^S$	*P. aeruginosa*	0.19/0.39	0.78/0.78	25.00/50.00	1:32/1:16	33	No
26	3rd Metatarsal-phalangeal joint/4A	*P. aeruginosa*	0.10/0.19	3.13/6.25	12.50/25.00		27	No
45	1st Metatarsal-phalangeal joint/4A	*P. aeruginosa*	0.39/3.13	1.56/6.25	50.00/100.00	1:16/1:2	2	No
30	Tibia/4A	*E. coli* *Peptostreptococcus anaerobius* *Peptococcus prevotti* *Peptococcus magnus*	1.56/3.13	0.10/0.10	1.56/1.56	1:16/1:4	38	No
28	Tibia/4A	*E. coli*	1.56/1.56	0.10/0.19	3.13/3.13	1:16/1:4	25	No

[a] See Materials and Methods for a description of the classification system used for determining stage of disease.
[b] G, Growth in concentrated serum.

second episode of osteomyelitis revealed *Escherichia coli*, *Enterococcus* sp., and *P. mirabilis*. The second course of therapy included several debridements, myocutaneous coverage, new cancellous bone grafts, and 36 days of treatment with parenteral administration of ampicillin and cefotaxime. The osteomyelitis remains arrested 8 months after completion of therapy. The initial treatment failure was considered secondary to central graft necrosis in a locally compromised extremity.

A 25-year-old male developed stage $4B^L$ osteomyelitis 1 month after suffering a grade III open fracture (6) of his tibia and fibula in a motor vehicle accident. At the time of internal fixation and free flap coverage, *E. cloacae* and *P. maltophilia* were cultured. Large segments of dead cortex were left in the wound for fixation purposes. The fibula was transferred to the tibia as a bypass graft for stability purposes. The patient received 36 days of ceftazidime treatment. At 4 months after completion of therapy, pain, swelling, and drainage recurred. The fibular bypass was healed. A bone biopsy culture revealed *E. cloacae*, *Enterococcus* sp., and *Staphylococcus aureus*. The patient chose to undergo a below-the-knee amputation rather than undergo a prolonged course of antibiotic treatment and reconstruction.

The third failure occurred in an obese 46-year-old woman. Her past medical history included an open pelvic fracture, a resolved wound infection, subsequent hip joint deterioration over the ensuing 8 years, and a total hip arthroplasty 1 year before admission to UTMB. The femoral component was press fitted, and the acetabular cup was cemented into position. The patient was admitted with an infected total hip arthroplasty ($4B^S$ osteomyelitis). There was no evidence of component loosening. A hip aspirate culture yielded *E. cloacae*. She was treated for 42 days with parenteral ceftazidime without prothesis removal. It was explained to her that the chances of arresting the infection with the prothesis in place were small but that the disability after removal of the prothesis would be great. The MIC and MBC of ceftazidime for this organism were 1.56 and 3.13 μg/ml, respectively. At 5 months after the completion of therapy pain recurred. At the time of prosthesis removal and debridement, *E. cloacae* was again isolated. The MIC and MBC of ceftazidime for this organism were 1.56 and 12.5 μg/ml, respectively. The major reason for treatment failure was the retained, infected prosthesis. The patient was given 42 days of parenteral cefotaxime after prosthesis removal. The osteomyelitis remains arrested 12 months after completion of protocol therapy.

A patient treated with ceftazidime developed a pin tract infection with *P. aeruginosa* after completion of antibiotic therapy. This was felt to be a complication of his treatment and not a recurrence of disease.

At 1 month after ceftazidime therapy, another patient had a positive culture for *P. aeruginosa* at the time of augmentation of an open cancellous graft (Papineau). There was no erythema or drainage at the graft site, and the sedimentation rate was 6 mm/h. It was determined that the infection represented a colonization and not a recurrent osteomyelitis. The grafts healed, and the infection remains arrested 16 months after completion of therapy.

There were nine patients (males) treated with ticarcillin and tobramycin. The dosage of ticarcillin was 18 g per day. The dosage of tobramycin ranged between 100 to 360 mg/day. The optimal tobramycin dosage was based on weekly levels of tobramycin in serum. Duration of therapy ranged between 27 and 62 days (mean, 42 days). The mean age of patients in this treatment group was 36.3 years.

There were 12 organisms isolated from the nine patients (Table 2). *P. aeruginosa* was the most common organism isolated. A single organism was isolated in eight patients, and a single aerobic organism and multiple anaerobic organisms were isolated in one patient. The osteomyelitis was considered to be arrested in all nine patients at the end of initial therapy and on follow-up examinations. Follow-up time ranged from 2 to 38 months (mean, 22 months).

Very few side effects were manifested in this study. One patient receiving ceftazidime had a mild increase in serum

glutamic oxalacetic transaminase and serum glutamic pyruvic transaminase levels during therapy. His enzyme levels returned to normal by 1 month after completion of therapy.

The MICs of ceftazidime and tobramycin for 90% of all *P. aeruginosa* isolated from osteomyelitis patients at UTMB over the 18-month duration of this study were 12.5 and 6.25 μg/ml, respectively. A total of 90% of the isolates were susceptible to ceftazidime, and 86% of the isolates were susceptible to tobramycin.

DISCUSSION

Contiguous-focus osteomyelitis is usually a polymicrobic infection that includes aerobic gram-negative rods. However, hematogenous osteomyelitis may also be caused by gram-negative organisms especially in the intravenous drug abuser population. Ceftazidime is a new extended-spectrum cephalosporin with enhanced activity against aerobic gram-negative rods, including *P. aeruginosa*. Osteomyelitis was arrested in nine of nine patients (100%) receiving tobramycin and ticarcillin and in only six of nine patients (67%) receiving ceftazidime after the initial course of therapy. A conclusion concerning the efficacy of ceftazidime versus tobramycin and ticarcillin cannot be made because of the limited number of patients in each treatment.

The treatment groups were equivalent in age, sex, and anatomic stage. However, the ceftazidime group had five compromised hosts compared with one for the ticarcillin-tobramycin group. The ceftazidime treatment failures may be related to inadequate surgical debridement, failure to remove hardware, and antibiotic failure. If the two presumed surgical failures are removed from consideration, the arrest rate of ceftazidime is six of seven (86%). All treatment failures occurred in patients with stage 3B or 4B osteomyelitis. Bactericidal levels of the drugs in the serum were not predictive of outcome.

Enterococcus sp. was isolated from bone culture in two of the three treatment failures. Overgrowth with *Enterococcus* sp. may be a complication of long-term extended-spectrum cephalosporin use.

Ceftazidime appeared to be as safe as the combination of tobramycin and ticarcillin. One patient receiving ceftazidime had a mild increase in liver transaminases. Similar changes have been reported with other cephalosporins (10, 13).

The ultimate criterion for clinical and bacteriological cure of osteomyelitis will require prolonged follow-up. Because of its chronic and variable course, osteomyelitis is a difficult infection to evaluate. Continued infection may be occult and not manifest for years. Our results showed that debridement and high dosages of ceftazidime for 4 to 6 weeks were associated with three treatment failures. No treatment failures were seen with the combination of tobramycin and ticarcillin. This study is compromised by the small number of patients and by limited follow-up. One of our patients suffered a relapsed 18 months after completing his antibiotic treatment. A second study had not confirmed this observation that ticarcillin and tobramycin seem to be more effective than ceftazidime for the treatment of gram-negative osteomyelitis (D. J. Sexton, C. G. Wlodaver, L. E. Tobey, A. L. Finn, and J. M. Chubb, Program Abstr. 24th Intersci. Conf. Antimicrob. Agents Chemother. abstr. no. 1213, 1984). Further controlled studies and 3- to 5-year follow-ups are necessary to further define this observation.

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