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Treatment of Hospitalized Patients with Complicated Skin and Skin Structure Infections: Double-Blind, Randomized, Multicenter Study of Piperacillin-Tazobactam versus Ticarcillin-Clavulanate

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We compared the efficacy and safety of two β-lactam–β-lactamase inhibitor combinations, namely, piperacillin-tazobactam and ticarcillin-clavulanate, in the treatment of complicated bacterial infections of skin that required hospitalization. The study was a randomized, double-blind, comparative trial involving 20 centers. The infections were classified as (i) cellulitis with drainage, (ii) cutaneous abscess, (iii) diabetic or ischemic foot infection, and (iv) infected wounds and ulcers with drainage. The clinical response rates were comparable for the two treatment regimens (61% of the patients were cured with piperacillin-tazobactam and ticarcillin-clavulanate and improvement was seen in 15 and 16% of patients treated with piperacillin-tazobactam and ticarcillin-clavulanate, respectively). Both regimens were found to be safe and well tolerated. These data support the use of piperacillin-tazobactam for initial empiric therapy of hospitalized patients with complicated skin and skin structure infections.

Bacterial infections of the skin and its structures are common clinical problems. They range from mild pyodermas to life-threatening infections. *Staphylococcus aureus* and *Streptococcus pyogenes* are the most common causes of mild superficial skin infections which can usually be treated with oral antimicrobial agents. However, deeper, more extensive, and more indolent infections may require more aggressive intervention such as drainage, debridement, and systemic antimicrobial therapy. Examples include diabetic foot infections, deeper cutaneous or intramuscular abscesses, infected pressure or neuropathic ulcers, and postoperative or traumatic wound infections that are frequently due to multiple and more resistant organisms.

Piperacillin sodium, a semisynthetic penicillin with a broad spectrum of antibacterial activity, has been used widely in the treatment of serious infections (3, 7). One disadvantage of piperacillin is its susceptibility to β-lactamase inactivation. Tazobactam (CL 298,741), a newly developed β-lactamase inhibitor of the penicillanic acid sulfone class, irreversibly inactivates a wide range of bacterial β-lactamases (1). In vitro studies showed that ratios for the piperacillin-tazobactam combination of 8:1 and 16:1 were highly effective against β-lactamase-producing piperacillin-resistant isolates, namely, *Escherichia coli*, *Staphylococcus* sp., and *Bacteroides* spp. Concentrations of approximately 4 mg of tazobactam per liter in the blood are effective in inhibiting bacterial β-lactamase enzymes. A combination of 3 g of piperacillin and 375 mg of tazobactam (8:1 ratio) administered every 6 h was the dose selected to be compared with a β-lactam–β-lactamase inhibitor combination, ticarcillin-clavulanate, that has been shown to be effective in the treatment of skin and skin structure infections (2).

Piperacillin-tazobactam has been shown by Kinzig et al. (4) to achieve concentrations in skin and skin structures comparable or superior to those attained in plasma. Eighteen patients who underwent elective colorectal surgery received 4 g of piperacillin with 500 mg of tazobactam. Penetration was 5 to 10 times higher into skin than into fatty tissue and about 3 times higher than penetration into muscle tissue.

The multicenter study described here was designed to comparatively assess the safety, tolerance, and efficacy of piperacillin-tazobactam administered parenterally versus those of ticarcillin-clavulanate in hospitalized patients with complicated skin and skin structure infections caused by susceptible bacteria.

MATERIALS AND METHODS

The double-blind, randomized, comparative trial described here was conducted in 20 centers. Hospitalized

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patients 16 years of age and older with complicated skin or skin structure infections were randomly assigned, using a computer-generated schedule, to treatment with either piperacillin-tazobactam or ticarcillin-clavulanate in a 3:2 ratio. A 3:2 randomization ratio was selected to allow enrollment of more patients in the piperacillin-tazobactam arm of the study in order to provide a larger safety data base for registration of this compound. The categories of infection for which patients were eligible to be enrolled included cellulitis with drainage or fluid collection, cutaneous abscess, wound infection including acutely infected pressure ulcers and other traumatic wound infections, ischemic or diabetic foot infections, and acute infections of decubitus ulcers. Patients were required to present with purulent drainage or collection and at least three of the following: temperature greater than 38°C, peripheral leukocyte count greater than 10,000/mm^3 with greater than 5% immature neutrophils, local erythema, local swelling, tenderness, pain, or fluctuance. The severity was assessed by the investigator as mild, moderate, or severe at the baseline.

Patients with any of the following were excluded: known or suspected hypersensitivity to beta-lactam antibiotics or β-lactamase inhibitors; moderate to severe renal dysfunction; evidence of active liver disease; peripheral granulocyte counts of <1,000/mm^3 or platelet counts of <50,000/mm^3; receipt of more than two doses of another antibacterial agent within 72 h prior to enrollment; receipt of another investigational drug within 1 month prior to enrollment; active or treated leukemia; AIDS; the need for hemodialysis, peritoneal dialysis, plasmapheresis, or hemoperfusion; osteomyelitis contiguous with a skin or skin structure infection; potential requirement for amputation of the infected area; pressure ulcer infections of greater than 2 weeks' duration (because of the known difficulty in eradicating organisms from chronic decubitus ulcers); and a concomitant infection other than the skin and skin structure infection.

Patients were dosed every 6 h with either piperacillin-tazobactam, 3 g and 375 mg, respectively, or ticarcillin-clavulanate, 3 g and 100 mg, respectively, for a minimum of 5 full days and for at least 48 h after the resolution of signs and symptoms. Patients were seen and examined at all protocol-specified times, including the posttreatment visits.

Surgical debridement or drainage was allowed and was accepted as an integral part of patient management. The need for surgery and the need for other adjunctive therapy was determined by the investigator and the collaborating surgeon.

Patients were evaluated for their clinical responses to therapy daily for the duration of treatment in the hospital, at 24 to 72 h after the completion of therapy (early follow-up), and at 10 to 14 days after the completion of therapy (late follow-up). The endpoint evaluation recorded in subsequent tables represents the last follow-up obtained for a given patient. Clinical outcomes were as follows: cured, which was defined as a patient who completed at least 5 days of therapy and who showed complete recovery from an acute infection; and improved, which was defined as a patient who showed improvement in at least three of the following parameters when compared with the values of those parameters obtained at the preenrollment evaluation: quantity of drainage, erythema, severity of swelling, tenderness, pain, fluctuance, lymphangitis, rigors, temperature, peripheral leukocyte count. For patients categorized as improved, incomplete resolution of the skin and skin structure infection could be seen, but the patients were clearly considered to have shown improvement by the clinician and did not require new antimicrobial therapy. Responses of cured and/or improved were considered favorable. Unfavorable responses included relapse, which was defined as a patient who showed initial improvement with subsequent worsening of any of the parameters described above, or failure, which required a change in antimicrobial therapy.

For purposes of registration of the drug, amputations and changes in antimicrobial therapy prior to the protocol-specified follow-up times were termed clinical "failures," regardless of the investigator's determination that a clinical cure or improvement in the infection might have occurred. These are termed the "registration criteria"-based outcome determinations. We also used the investigator's clinical assessments at the end of therapy and termed them the "revised" outcome determinations. Both methods of outcome determination assessment are used in this report to deal with patients undergoing amputation or changes in antimicrobial therapy.

Evaluation of bacteriological outcome was performed in the following manner. Both aerobic and anaerobic cultures of material draining or aspirated from the infected area were to be obtained within the 48 h prior to the start of therapy. Blood for cultures was also to be drawn from all patients. Cultures of samples from infected areas were to be repeated during the course of therapy and at follow-up if the clinical conditions warranted repeat testing or if infected material was available for culture. The following outcomes were recorded for bacteriological efficacy: eradication, which meant that all baseline pathogens were eradicated; eradication presumed, which meant that the patient's clinical response was favorable (cured or improved) and there was no material available for culture; persistence, which meant that one or more pathogens obtained initially at the baseline were present in cultures of samples taken at follow-up; persistence presumed, which meant that the patient had an unfavorable clinical response but that purulent material was not available for culture or a sample for culture was not taken (this response was grouped with persistence as an unfavorable outcome); and superinfection, which was defined as one or more new pathogens present in cultures taken at follow-up and a clinical course consistent with an infection that required additional or different antimicrobial therapy.

Prior to enrollment of the first patient in the study, criteria by which patients would be considered evaluable for assessing efficacy for registration of the drug were established. A patient was considered evaluable if each of the following criteria was met: a pretherapy pathogen susceptible to either study drug was present, susceptibility data for at least one pathogen were available, no other antibacterial agents were administered concomitantly during the study, there were at least 5 days of treatment with the study medication (to qualify for a favorable outcome), and the patient underwent at least one posttherapy follow-up (to qualify for a favorable outcome). For an unfavorable outcome, at least 3 days of therapy were required.

The issue of bias introduced into the subset of evaluable patients by the imposition of the evaluability criteria stated above was addressed by a separate analysis of all treated patients by using the investigator-assigned clinical outcome at the endpoint as the analysis parameter (i.e., intent-to-treat analysis).

Null hypotheses and sample sizes, and power considerations. Null hypotheses of no (zero) treatment difference were associated with all statistical tests, and all testing was performed in the two-tailed mode at the alpha = 0.05 level of significance.

TABLE 1. Demographic characteristics and diagnoses for all treated patients and evaluable patients

Characteristic	Piperacillin-tazobactam		Ticarcillin-clavulanate	
	All patients	Evaluable patients	All patients	Evaluable patients
Total no. (%) of patients	153 (100)	67 (100)	98 (100)	44 (100)
Mean age (yr)	53	53	52	55
Sex (no. [%])				
Male	115 (75)	53 (79)	69 (70)	32 (73)
Female	38 (25)	14 (21)	29 (30)	12 (27)
Race (no. [%])				
Caucasian	111 (73)	43 (64)	69 (70)	29 (66)
Black	29 (19)	12 (18)	20 (20)	8 (18)
Other races	13 (8)	12 (18)	9 (9)	7 (16)
Diagnosis				
Cellulitis	55 (36)	15 (22)	31 (32)	9 (20)
Cutaneous abscess	35 (23)	18 (27)	18 (18)	11 (25)
Diabetic foot, ischemic	32 (21)	18 (27)	31 (32)	17 (39)
Wound infection	31 (20)	16 (24)	18 (18)	7 (16)

TABLE 2. Primary reason for nonevaluability by treatment group among all treated patients

Nonevaluability reasons	No. (%) of patients		
	Piperacillin-tazobactam	Ticarcillin-clavulanate	Total
Failure to meet criteria for diagnosis	14 (9.2)	10 (10.2)	24 (9.6)
No baseline pathogen	18 (11.8)	6 (6.1)	24 (9.6)
Inadequate clinical follow-up	14 (9.2)	8 (8.2)	22 (8.8)
Prestudy antibiotic	10 (6.5)	8 (8.2)	18 (7.2)
Concomitant infection	7 (4.6)	7 (7.1)	14 (5.6)
Resistant pathogen at baseline	6 (3.9)	4 (4.1)	10 (4.0)
Other[a]	17 (11.1)	11 (11.2)	28 (11.2)

[a] Includes incorrect diagnosis, inadequate drug susceptibility data, inadequate bacteriologic follow-up, or inadequate treatment regimen.

The trial design specified sample sizes of $n_1 = 150$ patients randomized to piperacillin-tazobactam and $n_2 = 100$ patients randomized to ticarcillin-clavulanate. It was estimated that approximately 50% of the randomized patients would be evaluable for the primary analyses of efficacy; all treated patients would qualify for the intent-to-treat analysis. The projected numbers of evaluable patients provided a power of 70% for declaring an observed treatment difference that was statistically significant (alpha = 0.05, two-tailed) if the true treatment difference in the underlying populations was no more than 20%. For an intent-to-treat analysis, the projected numbers of treated patients provided a power of 82% for declaring an observed treatment difference that was statistically significant (alpha = 0.05, two-tailed) if the true treatment difference was no more than 15%.

RESULTS

Study population. There were 251 patients (184 men and 67 women) in 20 centers enrolled and treated in the present study. Table 1 summarizes the demographic data and the clinical diagnoses for all treated and evaluable patients in the study. The distribution of patients by race and sex was comparable between the two treatment arms ($P = 0.49$ and $P = 0.94$, respectively), and the mean ages among all treated patients were similar ($P = 0.89$). Differences in the distributions of clinical diagnoses were not significant between the two treatment arms. Infections were community acquired in 85% of the patients in the piperacillin-tazobactam group and 91% of the patients in the ticarcillin-clavulanate group. Of the evaluable patients, 42% (28 of 67) of the piperacillin-tazobactam-treated patients and 27% (12 of 44) of the ticarcillin-clavulanate-treated patients had monomicrobial infections, and 58 and 73% had polymicrobial infections, respectively.

The mean duration of treatment of patients in the piperacillin-tazobactam treatment group was 8.2 days for all treated patients and 10.2 days for the 67 evaluable patients. The mean duration of treatment in the ticarcillin-clavulanate treatment group was 9.1 days for all treated patients and 10.5 days for the 44 evaluable patients.

Each investigator was asked to assess empirically the severity of infection and classify it as "mild," "moderate," or "severe" on the first day of treatment. These observations represented the blinded judgments of experienced clinicians. For all patients enrolled in the study, 96% in either treatment arm had infections that were graded as moderate or severe (48% of all infections in the piperacillin-tazobactam arm and 46% in the ticarcillin-clavulanate arm were considered to be severe). Among the evaluable patients treated with piperacillin-tazobactam, 52% had infections that were classified as severe and 45% had infections that were classified as moderate. Among the evaluable patients treated with ticarcillin-clavulanate, 43% had infections that were classified as severe and 52% had infections that were classified as moderate.

Evaluability. Among the 153 patients enrolled in the piperacillin-tazobactam arm, 67 (44%) were considered evaluable. Among the 98 patients enrolled in the ticarcillin-clavulanate arm, 44 (45%) were considered evaluable. The following were major reasons for declaring patients to be not evaluable (Table 2): the patient did not meet the protocol-specified criteria for a skin and skin structure infection (most commonly because of the absence of drainage or fluid collection) (9.6%), a negative baseline culture (9.6%), receipt of other or additional antimicrobial agents prior to enrollment in the study (7.2%), failure to report a clinical outcome (8.8%), or other miscellaneous reasons, which are summarized in Table 2 (11.2%). The frequencies of these events were comparable between the two treatment regimens.

Cellulitis was the most common diagnosis in patients enrolled in the study and was commonly associated with nonevaluability. It occurred in 85 (34%) of the 251 enrolled patients. The intent of the study was to enroll patients with complicated cellulitis with drainage or a collection of fluid associated with it. Cellulitis is a superficial infection often without associated drainage or fluid collection, making positive cultures less common than with most other cutaneous infections. In the present study, only 28% (24 of 85) of the patients diagnosed with cellulitis were found to be evaluable. Of the nonevaluable patients, 56% (34 of 61) were found to have negative cultures at the time that the original baseline culture was obtained.

Clinical outcome. Table 3 shows the clinical outcomes for the evaluable patients categorized by diagnosis and treat-

TABLE 3. Favorable clinical responses at endpoint for evaluable patients

Diagnosis and outcome	No. of patients with a favorable response/no. of patients with the diagnosis (%)		
	Piperacillin-tazobactam	Ticarcillin-clavulanate	*P* value[b]
Cellulitis			
Cured	10/15 (67)[a]	7/9 (78)	
Improved	2/15 (13)[a]	0/9 (0)	
Favorable	12/15 (80)	7/9 (78)	1.00
Cutaneous abscess			
Cured	15/18 (83)	8/11 (73)	
Improved	2/18 (11)	2/11 (18)	
Favorable	17/18 (94)	10/11 (91)	1.00
Diabetic or ischemic foot			
Cured	7/18 (39)	6/17 (35)	
Improved	5/18 (28)	4/17 (24)	
Favorable	12/18 (67)	10/17 (59)	0.90
Wound or ulcer infection			
Cured	9/16 (56)	6/7 (86)	
Improved	1/16 (6)	1/7 (14)	
Favorable	10/16 (63)	7/7 (100)	0.17
Total			
Cured	41/67 (61)	27/44 (61)	
Improved	10/67 (15)	7/44 (16)	
Favorable	51/67 (76)	34/44 (77)	1.00

[a] Favorable clinical response (cured and improved).
[b] Chi-square test with continuity adjustment.

ment group. Overall, the incidence of what were considered to be favorable responses (viz., cured and improved) was 76% (51 of 67) in the piperacillin-tazobactam arm and 77% (34 of 44) in the ticarcillin-clavulanate arm. The poorest outcomes occurred, as would be expected, in the combined category of ischemic or diabetic foot infections, with a favorable response rate of 67% for patients treated with piperacillin-tazobactam and 59% for patients treated with ticarcillin-clavulanate.

Criteria were established, prior to enrollment of the patients in the study, to assess objectively the efficacies of the two treatments for registration purposes. Patients were considered to be clinical failures if they had an amputation of the site of infection, even if the amputation had been performed because of poor vascularity or other non-infection-related reasons and even if the infection was felt to be improved or cured by the investigator. Similarly, patients who were switched to antibiotics administered orally so that patients could be treated at home were also considered to be failures even if they had little or no clinical findings of infection at that time. These criteria were used to determine the frequency of favorable clinical outcomes shown in Table 3.

Table 4 provides a further analysis of five patients in the piperacillin-tazobactam arm and four patients in the ticarcillin-clavulanate arm who were declared clinical failures on the basis of registration criteria but who had improvement in or cure of their infections on the basis of the revised criteria by using the investigator's endpoint blinded clinical outcome determination.

Three patients in each treatment arm (patients 1-012, 3-088, and 13-527 and patients 1-003, 10-385, and 14-525) were considered clinical failures because the infected limb was amputated because of poor circulation, even though the investigator felt that the diabetic foot infection was improved or was cured. Two patients (13-481 and 13-488) with surgical wound infections treated with piperacillin-tazobactam and one patient (13-482) with cellulitis treated with ticarcillin-clavulanate showed clinical improvement or were cured but were switched to another antibiotic and were declared to be clinical failures for study registration purposes.

Table 5 provides an examination of the clinical evaluation of outcome at the end of therapy by using the criteria developed for registration. It also lists the outcomes made on the basis of the investigator's assessment at the time that the study drug was stopped (the revised criteria) and provides a statistical comparison of the differences between the treatment arms. Use of revised criteria would change the endpoint clinical outcome such that there is an 84% (56 of 67 patients) favorable clinical response rate in the piperacillin-tazobactam arm and an 86% (38 of 44 patients) favorable clinical response rate in the ticarcillin-clavulanate arm.

We noted that there was a higher failure rate (6 of 16 patients) among piperacillin-tazobactam-treated patients than among patients (0 of 7 patients) with wound or ulcer infections treated with ticarcillin-clavulanate. Six patients treated with piperacillin-tazobactam with wound or ulcer infections were termed clinical failures on the basis of the registration criteria. In analyzing these results, two patients (13-481 and 13-488) were considered to be either improved or cured before they were switched to another antibiotic. The remaining four patients had either a relapse or a superinfection. On the basis of the investigator's endpoint clinical assessment, 4 of 16 patients with wound or ulcer infections failed to respond to piperacillin-tazobactam treatment and 0 of 7 patients failed to respond to ticarcillin-clavulanate therapy.

Bacteriologic outcome. The organisms isolated from the evaluable patients and the frequency with which they were eradicated by therapy are shown in Table 6. *Staphylococcus aureus* was the most frequently isolated pathogen in the present study. Among the evaluable patients treated with piperacillin-tazobactam, *Staphylococcus aureus* was a single pathogen in 39% (16 of 41 patients) and part of the polymicrobial flora in 61% (25 of 41 patients). For the evaluable patients treated with ticarcillin-clavulanate, *Staphylococcus aureus* was a single pathogen in 23% (6 of 26 patients) and was a component of the polymicrobial flora in 77% (20 of 26 patients). The eradication rates among evaluable patients with monomicrobial infections for *Staphylococcus aureus* were 75% (12 of 16 patients) and 50% (3 of 6 patients) for the piperacillin-tazobactam and ticarcillin-clavulanate treatment groups, respectively. The eradication rates for *Staphylococcus aureus* among patients with polymicrobial infections were 68% (17 of 25 patients) and 80% (17 of 20 patients), respectively, for the piperacillin-tazobactam and ticarcillin-clavulanate treatment groups. There were no statistically significant differences in the eradication rates between the two treatment arms ($P = 0.54$ for monomicrobial infections and $P = 0.33$ for polymicrobial infections).

Table 7 shows a correlation between the clinical and bacteriologic outcomes in all evaluable patients from whom *Staphylococcus aureus* was isolated. A total of 29 of 41 patients in the piperacillin-tazobactam arm and 20 of 26 patients in the ticarcillin-clavulanate arm had favorable clinical outcomes, and *Staphylococcus aureus* was eradicated from these patients. Two patients in each arm had favorable clinical outcomes, but their *Staphylococcus aureus* persisted.

TABLE 4. Patients termed "clinical failures" with evidence of clinical improvement during treatment with piperacillin-tazobactam or ticarcillin-clavulanate

Treatment group and patient no.	Skin infection	Underlying diseases	Severity of infection	Bacterial pathogen(s)	Endpoint clinical assessment	Comment
Piperacillin-tazobactam						
1-012	Diabetic foot infection	Signs of ischemia of foot	Severe	*Proteus mirabilis*, *Enterococcus faecalis*	Improved	Improved clinically but amputation on day 6 of therapy
3-088	Diabetic foot	Neuropathy; prior amputation	Severe	*Staphylococcus aureus*	Cured	Failure based on amputation on day 27 of therapy; no signs or symptoms
14-527	Diabetic foot infection	Possible neuropathy; needle in soft tissue	Moderate	*Citrobacter diversus*, *Klebsiella pneumoniae*	Improved	Amputation of toe on day 5 of therapy; clinical findings improved on day 4 of therapy
13-481	Wound infection	Poor circulation in leg for 1 year; anemia	Moderate	*Staphylococcus aureus*	Improved	Failed based on starting dicloxacillin and mupirocin on day 15 of therapy; signs and symptoms resolved prior to switch
13-488	Infected wound	Status post-open reduction internal fixation calcaneal fracture; exposed tendon; deep wound infection	Moderate	*Staphylococcus aureus*	Cured	Called a failure because patient was put on ceftriaxone 5 days after stopping study drug; investigator felt the patient was a clinical cure before the switch; Minimal signs and symptoms when ceftriaxone was started
Ticarcillin-clavulanate						
1-003	Diabetic	Osteitis; foot infection	Severe	*Pseudomonas aeruginosa*, *Enterococcus* sp., group B *Streptococcus* sp.	Improved	Amputation on day 8 of therapy; no improvement prior to amputation; purulent drainage persisted
10-385	Diabetic foot infection	Metastatic melanoma; gangrene of left third toe	Severe	*Citrobacter freundii*, *Enterobacter clocacae*, *Staphylococcus aureus*	Cured	Failed after day 6 of therapy because of amputation on that day; improvement in signs and symptoms before amputation
14-525	Ischemic, diabetic foot infection	Diabetic; prior amputation	Moderate	Group B *Streptococcus* sp.	Improved	Clinically improved prior to amputation on day 6 of therapy
13-482	Cellulitis	Stasis dermatitis; steriod-induced Diabetes; rheumatoid arthritis	Moderate	*Serratia marcescens*, *Acinetobacter lwoffi*, *Enterobacter aerogenes*	Cured	Two infection sites; changed to ciprofloxacin 2 days after therapy was stopped; clinical findings resolved prior to antibiotic change

Ten patients in the piperacillin-tazobactam arm and four patients in the ticarcillin-clavulanate arm had unfavorable clinical outcomes (by registration criteria) and persistence of the infecting organism. Three patients in the piperacillin-tazobactam arm from this group (3-088, 13-481, and 13-488 described in Table 4) were felt by the investigator to be improved or cured. By using the revised clinical outcome determinations (representing the investigator's assessment of clinical outcome), favorable clinical outcomes were found in 34 of 41 (83%) patients with *Staphylococcus aureus* infections who received piperacillin-tazobactam and 22 of 26 (85%) patients who received ticarcillin-clavulanate.

Evaluation by intent-to-treat analysis. In order to assess the potential for either of the two treatment regimens for empiric use in patients with presumed complicated skin and skin structure infections, an intent-to-treat analysis was performed for all patients enrolled in the trial. The all-treated-patients analysis includes patients who had a nonevaluable

TABLE 5. Clinical outcomes at end of therapy for all evaluable patients

Analysis variable	No. (%) of patients		P value
	Piperacillin-tazobactam	Ticarcillin-clavulanate	
Responses			
Cure	41 (61)	27 (61)	
Improved	10 (15)	7 (16)	
Relapse	7 (10)	2 (5)	
Failure	9 (13)	8 (18)	0.96[a]
Favorable versus unfavorable response			
Favorable (Cure, improved)	51 (76)	34 (77)	
Unfavorable (relapse or failure)	16 (24)	10 (23)	1.00[b]
Favorable versus unfavorable response by revised assessment[c]			
Favorable	56 (84)	38 (86)	
Unfavorable	11 (16)	6 (14)	0.90[b]

[a] Wilcoxon test.
[b] Chi-square test.
[c] Refer to text (and Table 4) for details of patients who were reassessed.

clinical outcome determination but who were considered to be failures by default for analysis purposes. Eleven piperacillin-tazobactam-treated patients and three ticarcillin-clavulanate-treated patients were declared "default failures." The analysis showed that 79% of the 153 patients treated with piperacillin-tazobactam and 86% of the 98 patients treated with ticarcillin-clavulanate had either an improvement in or cure of their complicated cutaneous infections. The difference in favorable clinical responses between the two therapy arms among all treated patients was not statistically significant ($P = 0.50$). This analysis demonstrates that the difference in favorable clinical outcomes between the two treatment arms for all treated patients (7%) and for the evaluable patients (1%) was similar and that the use of our evaluability criteria imposed no bias on the interpretation of the clinical outcome.

TABLE 6. Endpoint eradication of bacterial pathogens isolated from the infected site in evaluable patients

Pathogen	No. of isolates eradicated/no. of isolates recovered (%)	
	Piperacillin-tazobactam	Ticarcillin-clavulanate
Staphylococcus aureus	29/41 (71)	20/26 (77)
Streptococcus spp.	35/38 (92)	21/23 (91)
Enterococcus spp.	4/6 (67)	8/9 (89)
Acinetobacter spp.	2/4 (50)	1/1 (100)
Citrobacter spp.	0/2 (0)	3/5 (60)
Enterobacter spp.	4/7 (57)	1/3 (33)
Escherichia coli	1/1 (100)	4/5 (80)
Klebsiella spp.	2/4 (80)	0/0 (0)
Proteus mirabilis	4/5 (80)	2/2 (100)
Proteus spp.	2/3 (67)	2/2 (100)
Pseudomonas aeruginosa	1/1 (100)	1/2 (50)
Other gram-negative rods	4/5 (80)	3/4 (76)
Bacteroides spp.	9/12 (75)	13/14 (93)
Peptococcus-Peptostreptococcus spp.	4/4 (100)	3/3 (100)
Other anaerobes	2/2	0/0
Total	103/135 (76)	82/99 (82.8)

TABLE 7. Correlation between clinical and bacteriologic outcomes at endpoint among evaluable patients with *Staphylococcus aureus* as a pathogen

Treatment group and clinical outcome	No. (%) of patients with the following bacteriologic outcome/ total no. of treated patients (%)	
	Eradication	Persistence
Piperacillin-tazobactam		
Favorable	29/41 (71)	2/41 (5)
Unfavorable	0/41 (0)	10/41 (24)
Ticarcillin-clavulanate		
Favorable	20/26 (77)	2/26 (8)
Unfavorable	0/26 (0)	4/26 (15)

Adverse experiences. Sixty-five of the 153 (42%) piperacillin-tazobactam-treated patients and 41 of the 98 (42%) ticarcillin-clavulanate-treated patients experienced at least one adverse event during the study. The most frequently reported drug-related adverse experiences involved the gastrointestinal tract, with 11% of the patients in each treatment group reporting adverse events in this organ system. Diarrhea was the most common drug-related adverse experience, with an incidence of 6.5% in the piperacillin-tazobactam group and 4.1% in the ticarcillin-clavulanate group. Overall, there were no significant differences in the incidence of drug-related adverse events between the two groups.

DISCUSSION

Skin and skin structure infections may be caused by organisms that transiently or permanently colonize the skin, or they may be caused by exogenous pathogens that enter as a result of disruption of cutaneous integrity. *Staphylococcus aureus* and streptococci, including group A, B, and G streptococci, are the most common pathogens in monomicrobial skin infections. Polymicrobial skin infections are usually caused by a mixture of aerobic and anaerobic organisms and are particularly common in patients with diabetes, decubitus ulcers, or wound infections (6). In clinical practice, empiric treatment often must begin before bacteriologic results are available. Such therapy must include antimicrobial agents which have activity against the most frequently recovered pathogens. Empiric therapy of skin infections likely to be due to mixed aerobic and anaerobic flora has usually required at least two antibacterial agents. The combination of a β-lactamase inhibitor with a broad-spectrum penicillin provides a wide spectrum of antimicrobial activity and allows for the empiric use of monotherapy for these complicated skin and skin structure infections.

The present study was a multicenter, double-blind, randomized study of piperacillin-tazobactam versus ticarcillin-clavulanate in hospitalized patients with a diagnosis of complicated skin and skin structure infections. Both treatment groups were similar with respect to their demographics and evaluability of the patients. The diseases of the patients included in the present study are representative of those seen in moderately to severely infected hospitalized patients with infections of skin and skin structures and encompassed a broad variety of skin infections, varying from those usually considered highly responsive to treatment (cutaneous abscess and cellulitis) to those that often have a poor clinical

response (ischemic or diabetic foot infections) (1). One indication of the complicated nature of these infections is that 78% of the piperacillin-tazobactam-treated patients and 84% of the ticarcillin-clavulanate-treated patients required some significant adjunctive therapy, mostly surgical excision, amputation, and/or debridement. The baseline pathogens isolated from the patients enrolled in the present study were similar for both groups and were representative of the types of pathogens seen in patients with these infections. *Staphylococcus* and *Streptococcus* species were the most frequently isolated pathogens. Approximately 40% of the patients had monomicrobial infections and 60% had polymicrobial infections. The relatively high incidence of polymicrobial infections is attributed to the observed frequency of ischemic or diabetic foot infections, cutaneous abscess, and wound infections.

Ticarcillin-clavulanate has been approved for use in the treatment of skin and skin structure infections caused by a variety of susceptible pathogens. In a review of the published literature, File and Tan (2) reported a favorable clinical response to ticarcillin-clavulanate in 83 to 94% of reported skin and skin structure infections, whereas the favorable clinical response to the agents being compared was 75 to 89% (in four of the six studies) in the studies reported. They also reported an 89 to 91% bacterial eradication rate on the basis of data on file at SmithKline Beecham. Ticarcillin-clavulanate has also been shown to have a favorable safety profile (2). Given its safety and efficacy and given that it is the only currently approved antipseudomonal penicillin and β-lactamase inhibitor combination that can be administered parenterally, it was chosen as the comparative agent for the trial described here.

In the present study, favorable clinical outcomes on the basis of criteria developed for registration of the compound prior to dosing patients occurred in 76% of the piperacillin-tazobactam-treated patients and in 77% of the ticarcillin-clavulanate-treated patients. Although these were somewhat less favorable response rates than were obtained in the previously reported studies, they are comparable (2). When we reassigned outcome determinations on the basis of the investigator's assessment of clinical outcome at the end of therapy, the revised favorable outcomes were changed to 84% for piperacillin-tazobactam and 86% for ticarcillin-clavulanate, which are comparable to those in the published literature (2).

In the treatment of severe or moderately severe complicated skin and skin structure infections, initial empiric therapy with a broad-spectrum agent that is both safe and effective is critical and most commonly must be used in conjunction with surgical intervention. The present study showed that piperacillin-tazobactam treatment is as effective and safe as ticarcillin-clavulanate treatment for patients with complicated skin and skin structure infections caused by susceptible bacteria. It was more difficult to eradicate *Staphylococcus aureus*, primarily in patients with polymicrobial infections in which it was one among several aerobic and anaerobic pathogens. The somewhat lower rate of favorable clinical responses appears to reflect more the difficulty of treating ischemic or diabetic foot infections rather than a specific difficulty with *Staphylococcus aureus* alone. We believe that piperacillin-tazobactam is effective therapy when *Staphylococcus aureus* is suspected of being a pathogen.

It should be noted that in comparison with ticarcillin, piperacillin alone has better activity against *Enterococcus* spp. and a wider spectrum of activity against gram-negative rods, especially *Pseudomonas aeruginosa*. The addition of a β-lactamase inhibitor does not improve activity against *Enterococcus* spp. and class I β-lactamase (Richmond-Sykes)-producing organisms such as *Pseudomonas aeruginosa*, *Enterobacter* spp., *Serratia* spp., and *Acinetobacter* spp.; thus, the advantage of the intrinsic activity of piperacillin against *Pseudomonas aeruginosa* and *Enterococcus* spp. provides a potential advantage for the piperacillin-tazobactam combination compared with ticarcillin-clavulanate. The data presented here support the use of piperacillin-tazobactam for initial empiric therapy of hospitalized patients with complicated skin and skin structure infections, particularly in those in whom a mixed bacterial flora may be present.

REFERENCES

1. **Aronoff, S. C., M. R. Jacobs, S. Johenning, and S. Yamabe.** 1984. Comparative activities of the β-lactamase inhibitors YTR830, sodium calvulanate, and sulbactam combined with amoxicillin and ampicillin. Antimicrob. Agents Chemother. **26**:580–582.
2. **File, T. M., Jr., and J. S. Tan.** 1991. Ticarcillin-clavulanate therapy for bacterial skin and soft tissue infections. Rev. Infect. Dis. **13**(Suppl. 9):S733–S736.
3. **Fortner, C. L., R. S. Finley, and S. C. Schimpff.** 1982. Piperacillin sodium: antibacterial spectrum, pharmacokinetics, clinical efficacy and adverse efficacy and adverse reactions. Pharmacotherapy **2**:287–299.
4. **Kinzig, M., F. Sorgel, B. Brismar, and C. E. Nord.** 1992. Pharmacokinetics and tissue penetration of tazobactam and piperacillin in patients undergoing colorectal surgery. Antimicrob. Agents Chemother. **36**:1997–2004.
5. **Lipsky, B. A., R. E. Pecoraro, and L. J. Wheat.** 1990. The diabetic foot. Soft tissue and bone infection. Infect. Dis. Clin. N. Am. **4**:409–432.
6. **Sapico, F. L., H. N. Canawati, J. L. Witte, J. Z. Montgomerie, F. W. Wagner, Jr., and A. N. Bessman.** 1980. Quantitative aerobic and anaerobic bacteriology of infected diabetic feet. J. Clin. Microbiol. **12**:413–420.
7. **Winston, D. H., W. Murphy, L. S. Young, and W. L. Hewitt.** 1980. Piperacillin therapy for serious bacterial infections. Am. J. Med. **69**:255–261.