Treatment of Ventilator-Associated Pneumonia with Piperacillin-Tazobactam/Amikacin Versus Ceftazidime/Amikacin: A Multicenter, Randomized Controlled Trial

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In a randomized trial conducted in 27 intensive care units, we compared the clinical efficacy and safety of piperacillin-tazobactam (TAZ; 4 g/0.5 g q.i.d.) and of ceftazidime (CAZ; 1 g q.i.d.), both combined with amikacin (7.5 mg/kg b.i.d.), as therapy for ventilator-associated pneumonia (VAP; acquired after ⩾48 hours of mechanical ventilation). VAP was diagnosed with use of protected samples and quantitative cultures, and outcome was assessed blindly from treatment. Of 204 patients suspected of having VAP and randomized to a treatment arm of the study, 127 (64%) had bacteriologically confirmed infections, of which 37% were polymicrobial and 32% involved *Pseudomonas aeruginosa;* 115 patients (51 TAZ and 64 CAZ recipients) remained evaluable as per protocol. Clinical/bacteriologic cure rates (TAZ vs. CAZ, 51% vs. 36%; 95% confidence interval of difference, −0.2% to 30.2%), and 28-day mortality rates (16% vs. 20%) were similar; however, fewer bacteriologic failures occurred with TAZ (33% vs. 51%; $P = .05$). We conclude that the two regimens were of equivalent clinical efficacy in therapy for confirmed VAP.

Nosocomial pneumonia is associated with substantial morbidity and mortality, especially for patients in intensive care units [1–3]. While the severity of the underlying disease and acute illness of the affected patients largely account for this poor outcome, improvements might be expected from progress in antimicrobial therapy. The epidemiology of pneumonia acquired during mechanical ventilation (the so-called ventilator-associated pneumonia, or VAP) has been described in several recent studies [2, 4–7]. Most such infections are caused by gram-negative bacilli, especially *Pseudomonas* species, and up to 40% of cases are caused by polymicrobial infection [5, 7]. Prior antimicrobial therapy is a risk factor both for pneumonia and for infections with more difficult-to-treat organisms, leading to poor response to therapy and a poor outcome [6, 8–10].

The current approach to empirical antimicrobial therapy for VAP is use of a combination including a β-lactam drug and an aminoglycoside or one of the newer quinolones [11, 12]. Piperacillin-tazobactam (TAZ) is a new broad-spectrum β-lactam combination that could cover most organisms responsible for pneumonia acquired during mechanical ventilation [13], and its use may be a promising approach to therapy for patients having severe lower respiratory tract infection.

The diagnosis of VAP, however, is fraught with difficulties [14–16]. Results of various antibiotic strategies investigated are difficult to assess because the population studied is often ill-defined, combining patients with various presentations of lower respiratory tract infection, ranging from tracheobronchitis to severe pneumonia. The use of specific diagnostic techniques may allow more precise characterization of patients with VAP and more accurate selection of patients with VAP for inclusion in clinical trials [17–19].

In this clinical trial we compared the outcome of therapy with TAZ or ceftazidime (CAZ), both in combination with amikacin, in a well-defined group of intensive-care-unit patients having VAP, as confirmed by specific techniques using protected sampling procedures and quantitative cultures of respiratory tract secretions.

Patients and Methods

Design of study. This was an open, multicenter, randomized, controlled study conducted in 27 intensive care units in France, designed to test the hypothesis that TAZ and CAZ, both combined with amikacin, were of equivalent efficacy in the treatment of microbiologically confirmed VAP not caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

Study entry criteria. Patients hospitalized for ⩾72 hours and having undergone mechanical ventilation for at least 48 hours were eligible for inclusion in the study when clinically

Received 22 May 1997; revised 2 September 1997.

Grant support: Wyeth-Lederlé, France

This study was presented in part at the 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, held 15–18 September 1996 in New Orleans.

This study was conducted according to the French guidelines for human subjects experimentation. Written informed consent was obtained from all the patients or their parents, and the protocol was approved by the Comité Consultatif de Protection des Personnes dans la Recherche Biomédicale of Hospital Henri Mondor, Créteil.

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Clinical Infectious Diseases 1998; 26:346–54

1058–4838/98/2602–0014$03.00

suspected of having VAP. The criteria for clinical suspicion of VAP included all of the following: clinical signs of sepsis (new fever, increase in temperature over 38.2°C, or decrease below 36.5°C; and increase in WBC count to $>10{,}000/mm^3$); purulent tracheal aspirates; and a new infiltrate or otherwise unexplained persistence or worsening of preexisting infiltrates on chest radiographs.

Patients were not eligible if they were diagnosed as having AIDS, a hematologic malignancy, or severe neutropenia (<500 polymorphonuclear cells/mm^3) or had a history of documented allergy to β-lactam antibiotics. Likewise, patients were not eligible (1) if death was expected within 7 days of inclusion or a do-not-rescuscitate order had been written or (2) if they had a severity score (simplified acute physiology [SAPS II] score) [20] on inclusion higher than 50 and three or more organ failures [21] or a rapidly fatal underlying disease [22]. In addition, patients with suspected or documented tuberculosis, suspected or documented infection due to MRSA only, or a concomitant infection requiring other antimicrobial therapy (or that had necessitated the recent [<48 hours previously] introduction of antibiotics) were not eligible.

Microbiological diagnosis of VAP and secondary exclusions. The protocol required that one or several specific sampling techniques, followed by quantitative cultures, be used before inclusion of a patient in the study. Any one of the following three techniques was considered acceptable for obtaining respiratory tract secretions: bronchoalveolar lavage [23], protected specimen brush sampling via bronchoscopy [24], or protected telescoping catheter sampling performed blindly or via fiberoptic bronchoscopy [25].

Although therapy was often initiated because of a clinical suspicion of VAP, only patients with microbiologically confirmed VAP were subsequently retained in the primary efficacy analysis. The diagnosis of VAP was considered to be confirmed when the culture of at least one of the above three samples yielded bacteria at or above the required threshold for positivity for the technique (i.e., 10^3 cfu/mL for protected specimen brush or telescoping catheter sampling and 10^4 cfu/mL for bronchoalveolar lavage). Patients whose samples were sterile or yielded bacteria in a concentration below the required threshold were withdrawn from the study and secondarily excluded from the primary efficacy analysis. Patients whose samples yielded MRSA only were also secondarily excluded. However, patients having infection caused by both MRSA and other organisms susceptible to the assigned study drug regimen were given vancomycin in addition and were retained in the efficacy analysis.

Organisms recovered in cultures of respiratory tract secretions were identified in each hospital's clinical microbiology laboratory, and their susceptibility to the drugs used was tested with the disk-diffusion technique and breakpoints defined by the Antibiogram Committee of the French Society for Microbiology [26]. The MIC breakpoints used to define in vitro susceptibility and resistance, respectively, were as follows: piperacillin-tazobactam, ≤ 16 mg/L and >64 mg/L for *Pseudomonas aeruginosa* and ≤ 8 mg/L and >64 mg/L for all other species; ceftazidime, ≤ 4 mg/L and >32 mg/L; and amikacin, ≤ 8 mg/L and >16 mg/L. These values are slightly (one dilution) more stringent than those recommended by the National Committee for Clinical Laboratory Standards.

Drug regimens tested. Patients were randomized by center in blocks of four, according to a computer-generated randomization list, to receive a fixed combination of piperacillin and tazobactam (4 g of piperacillin and 500 mg of tazobactam q.i.d.) or ceftazidime (1 g q.i.d.), both in combination with amikacin (15 mg/[kg · d] in two divided doses for patients with normal renal function). The β-lactam drug was expected to be administered for 15 days, or up to 21 days for patients with difficult-to-treat organisms. Amikacin dosage was adapted to renal function according to nomograms and trough serum levels. Amikacin was expected to be given for at least 10 days to patients with infection involving *P. aeruginosa* and for at least 5 days to other patients.

Analysis

Populations analyzed. For purposes of analysis, three populations were defined: (1) the overall evaluable population, including all patients randomized and receiving at least one dose of the treatment regimen according to the protocol (this population was analyzed for assessment of the safety of the two regimens); (2) patients with VAP, including all patients with microbiologically confirmed VAP; and (3) patients evaluable as ''per protocol,'' including all patients with microbiologically confirmed VAP not due exclusively to MRSA and who had no major protocol violation. As only patients with confirmed pneumonia caused by organisms potentially susceptible to the regimens used were targeted in this study, the latter population was used for the primary efficacy analysis. We also analyzed outcome in the subpopulation not having coinfection with MRSA.

Endpoints of study and definitions. All case report forms from all patients randomized were reviewed by a Clinical Evaluation Committee (CEC), which examined the adequacy of criteria for inclusion and diagnosis of VAP and the clinical and microbiological data relevant to outcome; the CEC members were blind to the treatment group assignment. The primary endpoint was clinical cure at 6–8 days after the end of therapy, defined by the CEC as follows.

Cure was defined as complete or partial resolution of clinical signs and symptoms of pneumonia at the end of therapy, with no need for further antibiotic therapy during the 6–8 days of follow-up. Failure was defined as the need for a change in therapy during treatment or follow-up (including because of an adverse event); persistence, worsening, or relapse of clinical symptoms of VAP, whether or not associated with microbiological failure (i.e., documented persistence, relapse, reinfection, or superinfection); and/or death possibly or probably related to infection. Death was considered possibly or probably related to infection when it occurred during therapy or during the

follow-up period and was not due to an intercurrent event unrelated to the infection.

Other endpoints included evaluation of microbiological outcome, an analysis of mortality at end of therapy and at 28 days postrandomization, and an evaluation of the safety of the two regimens.

Statistical analysis. Quantitative variables are given as mean ± SEM, unless specified otherwise. Differences between groups were compared with Student's *t*-test or Wilcoxon's rank-sum test where appropriate for quantitative variables and with a χ^2 test (with Fisher's correction where appropriate) for qualitative variables. Survival analysis used the log-rank test. Comparison of the efficacy of the two regimens was made under the hypothesis of equivalence of the two regimens, with the assumption that TAZ would not be less effective than CAZ by >15%; this analysis used the 95% confidence interval of the difference of efficacy between the two drug regimens and a (unilateral) Dunnet-Gent test [27].

Assuming a secondary exclusion rate of 20% of randomized patients for lack of microbiological confirmation of VAP and a cure rate in the reference group of 60%, we planned to study a total of 160 patients with a clinical suspicion of VAP (we assumed a type one error of 5% and a type 2 error of 20%). Because the exclusion rate proved to be higher during the study, this number was subsequently increased to a projected 232 patients. Except for the analysis of equivalence between the two regimens, all other tests were bilateral. Risk factors for failure of therapy in the per-protocol population and in the subgroup with infection caused by susceptible organisms and no coinfection with MRSA were subjected to a stepwise logistic regression analysis, including variables significant by univariate analysis at a P level of ⩽.15. Variables retained in the final model were selected at a P level of ⩽.10.

Results

Populations analyzed. Of 204 patients randomized in the study, 197 received at least one dose of either drug regimen tested according to the protocol and were evaluable with regard to tolerance (98 TAZ and 99 CAZ recipients); 127 patients (64.5%) had microbiologically confirmed VAP (58 TAZ and 69 CAZ recipients). From this group, 12 patients were excluded because of infection caused by MRSA only ($n = 5$) or because of a major protocol violation ($n = 7$), i.e., use of concomitant antimicrobial therapy not allowed by the protocol. Thus, 115 patients (51 TAZ and 64 CAZ recipients) with confirmed VAP were evaluable as per-protocol, according to the CEC.

Clinical characteristics of patients with VAP upon inclusion (table 1). In all patients with confirmed VAP ($n = 127$), infection was diagnosed after a mean duration of mechanical ventilation of 11 days (median, 8 days), with two-thirds of cases (67%) occurring after 5 days (i.e., late-onset pneumonia); 76% of patients had received antibiotics prior to inclusion. A rapidly or ultimately fatal underlying disease, according to the McCabe and Jackson classification [22], was present in 32% of patients. The primary causes for respiratory failure leading to mechanical ventilation [17] are listed in table 1. In addition to respiratory failure, 17% of patients had one or more associated organ failure, according to criteria published by Knaus et al. [21]; 32 (25%) had severe sepsis; and 8 (6%) had septic shock. There was no major difference in the clinical characteristics of the 115 patients receiving TAZ or CAZ as per protocol, except for a predominance of males in the TAZ group (92% vs. 77%; $P = .02$) and a trend toward a higher frequency of severe sepsis in CAZ patients (32% vs. 20%; $P = .10$); however, the mean severity (SAPS II) score, which reflects the global severity of acute illness [20], was similar on inclusion (37 vs. 37.5; $P = .8$).

Microbiology of VAP. Each one of the three sampling techniques required by the protocol was used for microbiological confirmation of VAP episodes in approximately one-third of cases; 147 of 163 samples obtained upon inclusion of the 127 patients with confirmed VAP yielded organisms in significant growth on quantitative cultures. Infection was monomicrobial in 63% of patients; from 25% of patients two organisms and from 12% three or more organisms were recovered in significant growth. In the per-protocol population ($n = 115$), 170 organisms were recovered, with a similar distribution between the two treatment groups (table 2): gram-negative organisms accounted for 68% of the cases of pneumonia, gram-positive for 12%, and a combination of gram-positive and gram-negative for 20%. Four VAP episodes (3.5%) were associated with bacteremia. *P. aeruginosa* accounted for 25% of all organisms and contributed to infection in 32% of episodes; *Staphylococcus aureus* accounted for 12% of organisms, including two MRSA isolates (2%). About one-fourth of episodes were caused by common respiratory pathogens such as *Haemophilus influenzae* or *Streptococcus pneumoniae,* but only two patients had infection caused exclusively by members of the normal oropharyngeal flora. By disk-diffusion testing, 134 of 152 organisms tested (88%) and 122 of 151 (81%) were susceptible to TAZ and to CAZ, respectively, while 75.5% were susceptible to amikacin and only 66% to piperacillin.

Drug dosage received (per-protocol analysis). Patients randomized to the TAZ group received a mean ± SEM (range) daily dosage of 14.7 ± 0.3 (8–16) g of piperacillin, for a median duration of 15 (3–24) days; patients randomized to the CAZ group received a mean daily dosage of 3.8 ± 0.07 (1–6) g, for a median duration of 14 (2–25) days. For patients who remained in the study without early withdrawal (⩽4 days before the end of treatment), the median duration of treatment was 15.5 and 16 days in the TAZ and CAZ groups, respectively. The mean amikacin daily dosages were 14.8 ± 0.8 and 13.5 ± 0.6 mg/kg, respectively ($P = .4$), for a median duration of 9 (TAZ) and 8 (CAZ) days.

Outcome of Therapy

Clinical outcome: all patients with VAP. At 6–8 days posttherapy, the overall success rate was 48% in the TAZ group and 33% in the CAZ group (OR, 2.14; 95% CI, 0.5%–29.5%).

Table 1. Characteristics of all patients with ventilator-associated pneumonia (VAP) and of patients in the per-protocol analysis, at the time of their inclusion in the study.

Variable	All patients with VAP (n = 127)	Per-protocol analysis: treatment group		P value*
		TAZ (n = 51)	CAZ (n = 64)	
Mean age (y)	55.5 ± 1.5	52.3 ± 2.3	57.8 ± 2.1	0.1
Sex: no. of males/females	104/23	47/4	49/15	0.02
Severity of underlying disease [22]: no. (%) of patients				
Rapidly fatal	2 (1.5)	1 (2)	1 (1.6)	0.8
Ultimately fatal	39 (31)	14 (27)	21 (33)	
Nonfatal	86 (68)	36 (71)	42 (66)	
Primary cause of respiratory failure: no. of patients				0.2
Acute pulmonary edema				
Cardiogenic	15	6	7	
Noncardiogenic	5	1	4	
Post-trauma, burns	27	14	13	
Acute hypoventilation				
Central	32	16	11	
Peripheral	11	4	6	
Acute on chronic failure	10	1	8	
Pneumonia	4	1	3	
Shock	10	4	5	
Cardiorespiratory arrest	3	1	2	
Median LOS (d) in ICU†	8	7	8	0.3
Duration of mechanical ventilation†: no. (%) of patients				0.8
⩽5 d	42 (33)	17 (33)	20 (31)	
>5 d	85 (67)	34 (67)	44 (69)	
Prior antibiotic use: no. (%) of patients	96 (75)	39 (77)	48 (75)	
Organ system failure				
Mean no.	1.1	1.1	1.2	0.4
⩾2 Failures: no. (%) of patients	22 (17)	6 (12)	12 (19)	0.3
Severe sepsis: no. (%) of patients	32 (25)	10 (19.6)	20 (32.3)	0.1
Septic shock: no. (%) of patients	8 (6)	2 (4)	5 (8)	0.4
Serum creatinine (μmol/L)	102 ± 5	103 ± 9	102 ± 7	0.9
SAPS II	37.4 ± 1.5	37 ± 1.4	37.5 ± 1.6	0.8
Temperature (°C)	38.8 ± 0.09	38.9 ± 0.1	38.8 ± 0.1	0.3
PaO_2/FiO_2 ratio	209 ± 8	210 ± 12	204 ± 12	0.4
Blood leukocytes ($\times 10^9$/L)	13.1 ± 0.5	13 ± 0.7	12.9 ± 0.7	0.8

NOTE. Values are mean ± SEM, except as otherwise noted. CAZ = ceftazidime and amikacin; ICU = intensive care unit; LOS = length of stay; SAPS II = Simplified Acute Physiology Score II [20]; TAZ = piperacillin-tazobactam/amikacin.

* For comparison between CAZ and TAZ in per-protocol population.

† Before randomization.

Clinical outcome: per-protocol analysis. At the end-of-therapy assessment, 44% and 32% of TAZ and CAZ recipients, respectively, had no residual infiltrate on a chest radiograph (P = .2), and 50% and 38% were breathing spontaneously (P = .2). At follow-up 6–8 days post-therapy, 26 TAZ recipients (51%) and 23 CAZ recipients (36%) had a successful clinical and bacteriologic outcome, as assessed by the CEC; the difference in efficacy rate was 15% (OR, 1.85; 95% CI, −0.2%–30.2%), favoring TAZ recipients. Since the difference in efficacy rate did not exceed 15%, the two regimens were found to be of equivalent clinical efficacy, according to the hypothesis tested.

Analysis of treatment failures. According to the CEC, therapy failed for 25 (49%) and 40 (62.5%) of the TAZ and CAZ recipients, respectively (table 3). The outcome of therapy for one CAZ patient was judged as indeterminate because of an

Table 2. Microorganisms recovered from patients with VAP.

Microorganisms	No. (%) of patients from whom organism was recovered		
	All patients with VAP (n = 190)	Per-protocol analysis	
		TAZ group (n = 79)	CAZ group (n = 91)
Gram-negative			
P. aeruginosa	42 (22)	20 (25)	22 (24)
Pseudomonas species	2 (1)	0	1 (1)
Acinetobacter species	17 (9)	9 (11)	8 (9)
Proteus, Providencia, Citrobacter species	18 (9.5)	7 (9)	9 (10)
Haemophilus, Branhamella	19 (10)	9 (11)	8 (9)
Enterobacter, Serratia species	14 (7.5)	5 (6)	8 (9)
Klebsiella species	8 (4)*	3 (4)	5 (5.5)
Escherichia coli	11 (6)	2 (2.5)	9 (10)
Neisseria species	3 (1.5)	1 (1)	2 (2)
Gram-positive			
S. aureus	29 (15)	13 (16.5)	7 (8)
MRSA	7 (3.7)	2 (2.5)	0
Staphylococcus species	7 (4)	3 (4)	3 (3)
Pneumococci	6 (3)	1 (1)	4 (4)
Streptococcus species	14 (7.5)	6 (7.5)	5 (5.5)

NOTE. All microorganisms recovered from protected samples in VAP episodes are listed; 36% of episodes were polymicrobial. CAZ = ceftazidime and amikacin; MRSA = methicillin-resistant *Staphylococcus aureus;* TAZ = piperacillin-tazobactam and amikacin.

* One isolate was ceftazidime-resistant.

intercurrent event; this patient had pneumococcal pneumonia and received vancomycin for concomitant methicillin-resistant *Staphylococcus epidermidis* bacteremia, occurring 1 day after randomization. There were 8 and 7 nonmicrobiologically documented clinical failures in the two groups (TAZ vs. CAZ), ascribed to persistent or worsening clinical features of VAP leading to a change in antimicrobial therapy, and 17 and 33 failures, respectively, were associated with a poor microbiological outcome. Although the overall distribution of causes of failures was not different (P = .12), microbiological failures tended to occur less often with TAZ (33% vs. 51%; OR, 0.47; P = .05, χ^2 test).

Table 3 details the causes for therapeutic failure in both groups. Infection caused by organisms primarily resistant to the study drugs occurred at similar frequency with both regimens; all such patients were rapidly shifted to another therapy when the susceptibility data were obtained. Among patients remaining in the study, the rates of clinical and microbiological failures were 12/46 vs. 27/58, respectively, for TAZ and CAZ recipients (P = .023). This higher rate of failure recorded for CAZ recipients was essentially due to a twofold higher rate of lower respiratory tract superinfection (21% vs. 9%) and of persistence or relapse of infection with the initially infecting organisms (21% vs. 9%).

Factors associated by univariate analysis with failure of therapy in the per-protocol population were a rapidly or ultimately fatal underlying disease (P = .02) and the in vitro susceptibility of etiologic organisms to the therapy administered (P = .02); the treatment group was not significant (P = .12). Variables not associated with outcome of therapy were the inclusion SAPS II score, creatinine level, age, delay of onset of pneumonia, prior antibiotic use, PaO_2/FiO_2 ratio, or a microbial etiology (and presence) of *P. aeruginosa.* There was no association between duration of therapy and superinfection rates.

After correction for interactions between variables and for confounding factors, variables predicting a clinical failure that were retained in the multivariate model (at a P level of $\leqslant$.10) were the severity of the underlying disease (OR, 2.83; 95% CI, 1.1–7.25; P = .03), in vitro resistance to the drug regimen

Table 3. Outcome at 6–8 days post-therapy (per-protocol analysis) and causes of clinical and microbiological failures, according to the Clinical Evaluation Committee.

Variable	TAZ recipients (n = 51)	CAZ recipients (n = 64)
Clinical outcome, no. (%) of patients		
Cure	26 (51)	23 (36)
Failure	25 (49)	40 (62.5)
Indeterminate	0	1
Death (total, all outcome categories)	7	10
Clinical failure only, no. (%) of patients	8 (16)	7 (11)
Deaths	5	3
Primary clinical event associated with failure		
Persistence/worsening	6	4
Introduction of antibiotics	2	1
Adverse event and withdrawal	0	2
Clinical + bacteriological failure, no. (%) of patients	17 (33)	33 (51)
Deaths	2	7
Primary microbiological event associated with failure		
Primary resistance[†]	5	6
Persistence[‡]	4	8
Relapse[§]	0	4
LRT superinfection[‖]	4	12
Superinfection, other site	4	3

NOTE. CAZ = ceftazidime and amikacin; LRT = lower respiratory tract; MRSA = methicillin-resistant *Staphylococcus aureus;* TAZ = piperacillin-tazobactam and amikacin.

[†] Eight of 11 cases involved *Acinetobacter* species, and 3, *Pseudomonas* species; 1 was associated with LRT superinfection.

[‡] Nine of 12 cases involved *Pseudomonas* species (5 CAZ and 4 TAZ recipients), and 2 were due to gram-positive cocci; 5 (4 CAZ and 1 TAZ recipient) were associated with LRT superinfection.

[§] Two pseudomonas infections (1 associated with enterobacter superinfection), 1 infection due to gram-positive cocci only, and 1 enterobacter infection.

[‖] Caused by MRSA (7 cases, all in CAZ group), *Enterobacter* (3), *Acinetobacter* (2), *Xanthomonas maltophilia* (1), *Pseudomonas cepacia* (1), *S. aureus* (1), and *Aspergillus* species (1).

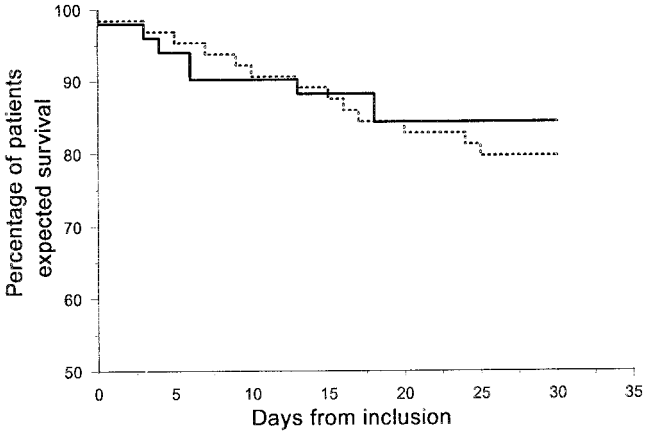

Figure 1. Probability of survival during the 28-day postrandomization period for patients with confirmed ventilator-associated pneumonia who received either piperacillin-tazobactam and amikacin ($n = 51$, *solid line*) or ceftazidime and amikacin ($n = 64$, *dotted line*), per protocol. There was no difference in the expected survival rates ($P = .55$, log-rank test).

received (OR, 2.16; 95% CI, 1.18–3.97; $P = .01$), a shorter delay of onset of pneumonia (OR, 0.96 per day; 95% CI, 0.92–1.0; $P = .10$), and treatment with ceftazidime (OR, 1.99; 95% CI, 0.88–4.54; $P = .10$). To further examine causes of failure during therapy, we restricted this analysis to evaluable patients who had confirmed VAP caused by organisms found susceptible in vitro to the administered β-lactam drug and who were not shifted to another therapy because of primary resistance; patients coinfected with methicillin-resistant staphylococci ($n = 4$) were excluded. In this subgroup of 99 patients, factors associated with a poor outcome of therapy were again the severity of underlying disease (OR, 2.68; 95% CI, 1.04–6.88; $P = .041$) and a shorter duration of mechanical ventilation before VAP (OR, 0.95; 95% CI, 0.89–1.0; $P = .051$); the trend toward a higher risk of treatment failure with ceftazidime therapy was confirmed (OR, 2.33; 95% CI, 0.99–5.48; $P = .052$).

Mortality. In the per-protocol population ($n = 115$), mortality at 6–8 days post-therapy was 14% in both groups, with 4 and 7 deaths attributed to infection in TAZ and CAZ recipients, respectively; at 28 days postrandomization, mortality was 16% (TAZ group) and 20% (CAZ group), and the probability of survival at 28 days was similar ($P = .55$) in the two groups (figure 1).

Safety

All 197 patients evaluable for safety received at least 2 days of therapy; 35% were treated for 2–7 days only, whereas 28% received therapy for >15 days. Adverse events were recorded in 37 of 98 TAZ recipients (49 events) and 38 of 99 CAZ recipients (46 events); the adverse events were judged severe in 24 TAZ and 17 CAZ recipients. The frequency and distribution by site of all adverse events recorded were similar in both groups. Nine TAZ recipients and 10 CAZ recipients had adverse events judged as definitely, possibly, or probably related to the test drug (18% and 22%; $P = .68$), including (in TAZ and CAZ recipients, respectively) hypereosinophilia (1 and 0), leukopenia (1 and 0), skin reactions (0 and 3), alteration in renal function (3 and 2), gastrointestinal tract disorder (1 and 0), and liver test abnormalities (4 and 4); treatment was interrupted because of a nonfatal adverse event in 3 and 4 patients, respectively. The overall 30-days-post-therapy mortality rate among all evaluable patients was 18.4% (18 of 98) in the TAZ group and 22.2% (22 of 99) in the CAZ group ($P = .55$).

Discussion

VAP remains a diagnostic and therapeutic challenge, and the prognosis for affected patients remains poor despite general awareness of the problem and the availability of several new antimicrobial agents [28]. In this study we chose to circumvent the problems associated with diagnostic criteria by using quantitative cultures of protected specimens to diagnose VAP. We thus selected a population most probably having definite pulmonary infection acquired during mechanical ventilation [10, 19]. In this well-defined population, we found that therapy with TAZ and amikacin was at least equivalent to the combination of CAZ and amikacin. However, both regimens were successful for ≤50% of patients with confirmed VAP, as assessed by the independent CEC members, who were blind to the treatment regimen.

Several factors related to the design and analysis of this study may account for this apparently unsatisfactory outcome, in comparison with results of other studies in this field. First, clinical trials of antimicrobial therapy for lower respiratory tract infection have often combined patients having community-acquired infection with patients having nosocomial infection. Even in trials restricted to patients with nosocomial infection, patients with pneumonia acquired during mechanical ventilation, such as ours, are usually combined with patients whose pneumonia was not acquired during such ventilation and with patients not undergoing mechanical ventilation at all [28, 29]. Finally, in such trials, it is common to include patients with ill-defined lower respiratory tract infections and to combine patients having tracheobronchitis (likely associated with a better outcome) with patients having pneumonia.

Most prior studies of nosocomial pneumonia have relied on tracheal aspiration to diagnose pneumonia in mechanically ventilated patients. Although probably very sensitive, such sampling lacks specificity [19, 30], and many patients included in such studies may have had tracheobronchitis rather than pulmonary infection per se [18]; often, no pathogen is isolated [31], which makes outcome assessment difficult. We used protected samples cultured quantitatively to diagnose VAP, thus

likely excluding patients with tracheobronchitis only. Accordingly, more than one-third of patients eligible and randomized because of a strong clinical suspicion of pneumonia, based on the usual clinical criteria, were secondarily excluded because of the lack of microbiological confirmation of VAP.

Although we excluded a priori patients with very severe acute illness or underlying disease, our inclusion criteria selected the population at highest risk of treatment failure and poor outcome [12], and we believe our results closely reflect the outcome of therapy for critically ill patients with VAP. A drawback of this approach is that an intention-to-treat analysis could not be used in the outcome evaluation, since most patients without microbiologically confirmed VAP had antibiotic therapy substituted or discontinued and were withdrawn from the study.

The criteria for assessment of outcome of therapy were also stringent. The interpretation of these was based on recommendations recently proposed by the Infectious Diseases Society of America [32]. For example, all cases in which new antibiotics were introduced were classified as treatment failures, irrespective of the reason for their introduction. Likewise, we did not exclude from the primary efficacy analysis those patients who were infected with organisms initially resistant to the allocated regimen and were switched to another regimen for this reason; although an intention-to-treat analysis was not used in this study, such patients were categorized as treatment failures, because this study sought to examine the overall outcome of therapy for patients with confirmed pneumonia due to organisms expected to be susceptible to the drug regimen tested.

In this randomized trial, the combination of TAZ and amikacin appeared at least as effective as the combination of CAZ and amikacin; the former regimen actually tended to be superior, with an overall cure rate of 48% (vs. 33%) and a twice-lower risk of treatment failure after multivariate analysis. As expected, treatment failures were associated, among other factors, with decreased susceptibility of the pathogens to the drug regimen received. The trend toward superior clinical efficacy of TAZ and amikacin was reinforced after multivariate analysis, when the analysis was restricted to patients having infection caused only by organisms initially susceptible to the administered β-lactam drug and no coinfection with methicillin-resistant staphylococci. However, the relatively small number of patients retained in this analysis does not allow firm conclusions in this regard, and this result would need confirmation in a larger study of appropriate design.

Treatment failures among CAZ recipients appeared essentially associated with a higher incidence of persistence of initial organisms or of reinfection and superinfection (table 3). Most failures recorded in ceftazidime recipients were associated with polymicrobial infection, and 45% of infections that responded poorly to CAZ were associated with *P. aeruginosa.* However, polymicrobial infection or infection with *P. aeruginosa* [28, 33] was not associated with treatment failure in the multivariate analysis of risk factors for therapeutic failure, after correction for confounding factors such as the severity of underlying disease and acute illness. It is noteworthy that a similar outcome of infection with *P. aeruginosa* was recorded in both treatment groups, with a 40% and 39% success rate, respectively, among TAZ and CAZ recipients; this suggests that both combination regimens were of similarly acceptable efficacy against *P. aeruginosa* infection.

One possible explanation for the higher rate of microbiological failures could be the relatively low ceftazidime dosage. Some authorities recommend that adult patients with infections that are severe or due to difficult-to-treat organisms be given a higher ceftazidime dosage (i.e., 6g/d) than that used in this study (4 g/d), so that drug levels are maintained well above the MIC for organisms targeted; likewise, continuous administration of ceftazidime has been suggested to improve efficacy and prevent emergence of resistance during therapy [34]. Despite these theoretical grounds, it remains unproven that high ceftazidime dosages result in improved cure rates among non-neutropenic patients. We used an intermediate dosing regimen of 1 g q.i.d. in patients with normal renal function, which should provide sufficient 24-hour coverage for susceptible pathogens; besides, the potential value of higher dosages probably applies more to monotherapy than to combined β-lactam/aminoglycoside therapy [31].

At least one study found a similar outcome (with an 86% overall clinical response rate) in a randomized trial of therapy for severe lower respiratory tract infection in patients in an intensive care unit (82% of whom were undergoing mechanical ventilation) that compared a 3-g/d dosage of ceftazidime to a 6-g/d dosage [35]. Finally, in a recent trial comparing TAZ to CAZ (2 g t.i.d.), both administered with tobramycin or amikacin, for the treatment of hospital-acquired lower respiratory tract infection, Joshi et al. [29] found results similar to ours: the clinical outcome was better for patients receiving the former combination (74% vs. 50%; $P < .01$), despite the fact that high doses of ceftazidime were administered.

Our results indicate that both regimens may be adequate empirical therapy for patients with suspected VAP when MRSA is not a likely causative organism. We do not suggest that such therapy be used and maintained for all patients with VAP, since unduly prolonged therapy with such broad-spectrum regimens may foster emergence of resistance and increase the rate of superinfection. The antibiotic regimen should eventually be adapted to organisms subsequently identified and to their antibiotic susceptibility; in patients having pneumonia proven to be caused by organisms susceptible to narrower-spectrum drugs (especially those patients with early-onset pneumonia), as observed in about one-fourth of patients included in this study, the initial empirical therapy should be replaced with such narrower-spectrum drugs.

Our study also underscores the fact that, when defined with strict criteria, VAP entails a high risk of treatment failure, mostly due to superinfection or reinfection, even when combination therapy is used. It should be emphasized that the diag-

nostic approach used in this study resulted in secondary exclusion of slightly more than one-third of patients randomized, a rate higher than the 20% anticipated. Accordingly, the planned inclusion total was increased by 30%, but the corresponding accrual rate could not be achieved within the planned time frame of the study.

These results emphasize the difficulties in the clinical evaluation of critically ill patients suspected of having pneumonia and the problems encountered in conducting clinical trials in this population when strict diagnostic criteria are used. The high exclusion rate weakens the inferences of this study, because the expected power was not achieved. Actually, our study had only a 50% chance of detecting a lack of equivalence between the two regimens in the confirmed-VAP group. Despite the limited power of our study, it is noteworthy that the difference in efficacy rate between the two regimens reached just the 15% threshold.

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