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ORIGINAL

Efficacy and tolerability of piperacillin/tazobactam versus ceftazidime in association with amikacin for treating nosocomial pneumonia in intensive care patients: a prospective randomized multicenter trial

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Abstract *Objective:* To compare clinical and bacteriological efficacy as well as tolerability of two regimens of broad-spectrum antibiotics (ceftazidime versus piperacillin/tazobactam) combined with amikacin in the treatment of nosocomial pneumonia in intensive care patients.
Design: Open label, prospective, multicenter, and randomized phase III clinical trial.
Setting: Medical or surgical intensive care units (ICUs) of nine acute-care teaching hospitals in Spain.
Patients and participants: One hundred and twenty-four ICU patients with nosocomial pneumonia and requiring mechanical ventilation were included. They were randomized to receive amikacin (15 mg/day divided into two doses) combined with either piperacillin (4 g every 6 h) and tazobactam (0.5 g every 6 h) ($n = 88$) or ceftazidime (2 g every 8 h) ($n = 36$).
Measurements and results: The causative pathogen was determined in 60.2 % of patients in the group of amikacin plus piperacillin/tazobactam and in 76.9 % in the group of amikacin plus ceftazidime. A total of 94 bacterial organisms were isolated among which gram-negative bacilli predominated, *Pseudomonas aeruginosa* being the most frequent. Clinical response at the end of antibiotic therapy was considered satisfactory (cure and/or improvement)

in 63.9 % of patients in the amikacin plus piperacillin/tazobactam group and in 61.5 % in the amikacin plus ceftazidime (odds ratio 1.1; 95 % confidence interval 0.44–2.75). Eradication or presumptive eradication rates for each pathogen and for either gram-negative or gram-positive bacteria were similar in both antibiotic combinations (odds ratio 1.2; 95 % confidence interval 0.39–3.66). A total of 21 adverse effects (23.9 %) occurred in the amikacin plus piperacillin and tazobactam group and six (16.7 %) in the amikacin plus ceftazidime group, thrombocytosis, renal dysfunction, and hepatic cytolysis being the most common. The efficacy and tolerability of the two therapeutic regimens were similar not only in the whole study population, but also in the subset of *P. aeruginosa*-related pneumonia (odds ratio 1; 95 % confidence interval 0.08–13.37).
Conclusions: Amikacin associated with either ceftazidime or piperacillin and tazobactam has shown comparable efficacy and tolerability in the treatment of ICU patients with nosocomial pneumonia.

Key words Pneumonia · Adult · Intensive care unit · Ceftazidime · Amikacin · Piperacillin/tazobactam

Introduction

Management of hospital-acquired pneumonia in severely ill patients usually requires admission to the intensive care unit (ICU) and ventilatory support, whereas in other patients, low respiratory infection develops as a complication of mechanical ventilation. Despite better understanding of the pathophysiology of this condition and systematic use of preventive measures, there has been an increase in the incidence of nosocomial pneumonia in relation to more severe conditions of hospitalized patients, use of more aggressive diagnostic and therapeutic procedures, and longer periods on mechanical ventilation [1, 2, 3].

In 40–50 % of the patients, nosocomial pneumonia is caused by multiple microorganisms, in particular *Pseudomonas aeruginosa, Staphylococcus aureus,* and *Enterobacteriaceae* spp [3, 4, 5, 6, 7, 8]. Identification of causative pathogens in mechanically ventilated patients is hampered by the low sensitivity and specificity of diagnostic methods especially in the presence of previous antibiotic therapy [9, 10, 11]. Empirical antibiotic treatment usually includes wide-spectrum bactericidal antimicrobials at maximum doses given as mono- or combined therapy. The combination of third-generation cephalosporins, especially ceftazidime and aminoglycosides, has been extensively used[12, 13, 14]. However, due to the appearance of class I β-lactamase, resistant strains have increased in recent years during treatment with ceftazidime, in particular in the case of gram-negative rods isolated from ICU patients [15, 16] which has made it necessary to use other first-line antibiotic agents. In fact, a substantial proportion of patients are already colonized by multiresistant bacteria when entering the ICU. Piperacillin/tazobactam is a broad-spectrum antibiotic of the ureidopenicillin family to which a β-lactamase inhibitor has been added. It is active against most *Enterobacteriaceae* organisms, *P. aeruginosa*, *Staphylococcus* spp including methicillin-susceptible *S. aureus*, and *Bacteroides* spp [17, 18, 19]. The association with aminoglycoside antibiotics, such as amikacin and tobramycin, increases the spectrum of activity and the bactericial effects of piperacillin/tazobactam against gram-negative bacteria including *P. aeruginosa* [20].

Piperacillin/tazobactam has been successfully used to treat severe nosocomial and community-acquired lower respiratory tract infections [21, 22, 23, 24, 25, 26]. This study was conducted to compare clinical and bacteriological efficacy as well as tolerability of two regimens of broad-spectrum antibiotics, that is, ceftazidime versus piperacillin/tazobactam combined with amikacin in the treatment of nosocomial pneumonia in intensive care patients.

Materials and methods

Nine ICUs in Spain participated in a prospective, open label, randomized, phase III study. The study was approved by the institutional review boards of the participating centers and by the 'Dirección General de Farmacia y Productos Sanitarios' of the Ministry of Health. The hypothesis of similar efficacy and tolerability of amikacin combined with either piperacillin/tazobactam (study group) or ceftazidime (control group) was tested. Because of greater clinical experience with the association of amikacin and ceftazidime, a randomization scheme of 2:1 for the study and control groups was established.

Participants

Patients of both sexes over 18 years of age admitted to the ICU were included in the study provided that the following criteria were met: length of hospital stay > 48 h without previous signs of infection; appearance of new clinical signs and symptoms suggestive of nosocomial pneumonia; detection of new and persistent radiological infiltrates or extension of previous infiltrates unrelated to any other diagnosis; signs of respiratory failure requiring mechanical ventilation ($PaO_2 < 90$ mm Hg, with $FiO_2 > 40\,\%$); and ICU admission.

The clinical criteria of suspicion of pneumonia were defined according to the definitions of the Centers for Disease Control and Prevention (CDC) [27] that included the presence of cough, purulent sputum, pleuritic chest pain, fever (> 38.2 °C) or hypothermia (< 36.5 °C), and leukocytosis ($> 10.0 \times 10^9$/l) or leukopenia ($< 5.0 \times 10^9$/l).

Pregnant and breast-feeding women were excluded as were patients with documented hypersensitivity to the study drugs or β-lac-

tam antibiotics; renal failure (serum creatinine concentration > 3.5 mg/dl or creatinine clearance < 20 ml/min); with antibiotic treatment within 72 h before inclusion in the study that were active against causative pathogens of pneumonia (except for cases of poor clinical evolution); need for concomitant administration of antibiotics that were active against causative pathogens of pneumonia; treatment with probenecid; leukopenia ($< 1.0 \times 10^9$/l) or thrombocytopenia ($< 50.0 \times 10^9$/l); liver dysfunction with increase of serum alanine and aspartate aminotransferase levels, alkaline phosphatase, and total bilirubin greater than three times the normal value; and massive bronchoaspiration of intestinal content. In addition, patients with a life expectancy of < 1 month and those with an order of no cardiopulmonary resuscitation in case of cardiac arrest were excluded.

All patients or their legal representatives signed the informed consent to participate in the study.

Microbiological diagnosis

Samples from the lower respiratory tract were obtained before the administration of antimicrobials by means of simple tracheal aspiration, protected specimen brush [28] or bronchoalveolar lavage (BAL) [29], which were blindly performed or directed by fiberoptic bronchoscopy. The etiology of pneumonia was confirmed when bacterial growth was detected in cultures of samples obtained at least by one of these procedures using $\geq 10^5$, $\geq 10^3$, and $\geq 10^4$ colony-forming units per milliliter (CFU/ml) as criteria for infection in samples recovered from tracheal aspirates, protected specimen brush, and BAL, respectively.

Causative pathogens were identified at the laboratories of clinical microbiology of the participating hospitals. Susceptibility testing was performed by the disk diffusion method using the cut-off points defined by the National Committee for Clinical Laboratory Standards [30]. The cut-off values for minimal inhibitory concentrations (MIC) used to define in vitro susceptibility and resistance of the bacteria isolated were as follows: ≤16 mg/l and > 64 mg/l for *P. aeruginosa* and ≤8 mg/l and > 64 mg/l for all other species in case of piperacillin/tazobactam; ≤4 mg/dl and > 32 mg/dl in case of ceftazidime; and ≤8 mg/l and > 16 mg/l in case of amikacin.

Treatment

Patients were randomized into blocks of six patients (four in the study group and two in the control group) using a computer-generated randomization list for each hospital. Patients assigned to the study group were given piperacillin 4 g and tazobactam 500 mg intravenously every 6 h. Patients in the control group received ceftazidime 2 g intravenously every 8 h. Amikacin 15 mg/kg of body weight was administered to patients in both groups. In patients with normal renal function, amikacin was divided into two daily doses, whereas in patients with renal impairment, the dose of amikacin was targeted to creatinine clearance values or drug plasma concentrations. Amikacin was administered at least for 10 days in patients with *P. aeruginosa* infection; in the remaining patients, amikacin was given at least for 3–4 days until microbiologic results confirmed the absence of *P. aeruginosa* in the cultures.

Variables

In all patients the following data were recorded: demographic characteristics; toxic history; underlying conditions; reason for admission to the hospital; clinical manifestations on a daily basis; chest radiographic features; and results of laboratory tests (blood cell count, coagulation tests, biochemical profile) and of bacteriological investigations before the onset of the study, repeated at least once a week in the course of treatment and until 14 days after completing the study. Severity of illness at the time of ICU admission was defined according to APACHE II scores [31]. Adverse effects were classified by the investigator as probably or possibly related to the study drugs when no other cause was found. Adverse effects were defined as severe when a specific treatment was required or if they were associated with worsening of the clinical conditions including death of the patient.

Clinical and microbiological definitions

A clinical evaluation committee, which was blind to the group to which patients had been assigned, reviewed the protocols of all patients randomized and confirmed the adequacy of inclusion criteria and completeness of clinical and microbiological data. Each patient was assessed within 24–72 h after the end of treatment and at 10–14 days thereafter.

Cure was defined as remission of pneumonia-related signs and symptoms; improvement as a favorable response with persistence of some of the signs and symptoms; failure as absence of response with persistence of clinical manifestations of pneumonia; relapse as reappearance of a new lower respiratory tract infection during the follow-up period; and not evaluable in case of protocol violation or withdrawal of treatment for any reason.

Microbiologically, eradication was defined as absence of organisms or negative culture of respiratory samples at the end of treatment (presumed eradication when a new culture was not necessary); persistence as positive blood and/or respiratory tract culture after completion of treatment; superinfection as identification of a new pathogen (different from that originally isolated) in the course of antibiotic treatment or immediately after treatment together with clinical manifestations of sepsis, septic syndrome, or septic shock; colonization as identification of a new pathogen in the course of treatment or immediately after treatment without clinical symptoms of sepsis; and not evaluable in case of protocol violation or withdrawal of treatment for any reason. At the 10–14 day assessment, relapse was defined as identification of the same causative pathogen and reinfection as identification of the same causative pathogen or a new microorganism with a different antibiotic susceptibility pattern.

Mortality was considered to be related to the lower respiratory tract infection when death occurred during the treatment period and the clinical and radiological signs of pneumonia persisted.

Statistical analysis

For the purpose of analysis, three populations were defined as follows: a) all patients who were randomized and who received at least one dose of the prescribed antibiotic regimen (tolerance and intention-to-treat analysis); b) patients with evaluable clinical response excluding protocol violations, early death (< 48 h after the initiation of treatment), isolation of pathogens resistant to some of the study drugs, and non-bacterial organisms; and c) patients with evaluable microbiologic response excluding patients in whom the causative pathogen was not identified. An intention-to-treat analysis in the subset of patients with infection caused by *P. aeruginosa* was also performed.

Continuous and categorical variables in the groups of piperacillin/tazobactam plus amikacin and ceftazidime plus amikacin were compared with the Student's *t*-test and the chi-square (χ^2) test,

Table 1 Reasons for exclusion in the piperacillin/tazobactam and ceftazidime arms of the study

	Piperacillin/tazobactam no. (%)	Ceftazidime no. (%)
Intention-to-treat	88	36
Reasons for exclusion	5 (5.7%)	10 (27.8%)
Lack of inclusion criteria	0	1
Death within the first 48 h	0	0
Protocol violation	1	2
Non-treatable microorganisms	2 (2.3%)	1 (2.8%)
Candida albicans	1	0
Aspergillus fumigatus	1	0
Legionella pneumophila	0	1
Microorganisms resistant to the study drugs	2 (2.7%)	6 (16.7%)
Acinetobacter baumannii	1	0
Staphylococcus aureus	1	2
Pseudomonas aeruginosa	0	2
Serratia marcescens	0	1
Enterococcus faecalis	0	1
Clinically evaluable patients	83	26
Bacteriologically evaluable patients	50	20

with Yate's correction or Fisher's exact test when needed [32]. Efficacy of the two therapeutic groups was analyzed on the basis of differences 20% or greater would have a probability (power) = 0.8 of being detected. The power calculation was based on the intention-to-treat population. Odds ratio and 95% confidence intervals were calculated. Survival was analyzed with the Kaplan-Meier method.

Results

The diagnosis of nosocomial pneumonia was established in 124 patients admitted to the ICUs of the participating hospitals, 88 were assigned to the piperacillin/tazobactam plus amikacin group and 36 to the ceftazidime plus amikacin group. However, five patients of the first group and ten of the second group were excluded from the analysis of efficacy. Reasons for exclusion are shown in Table 1. Therefore, 109 patients (piperacillin/tazobactam plus amikacin 83, ceftazidime plus amikacin 26) were evaluable for clinical response and 70 (piperacillin/tazobactam plus amikacin 50, ceftazidime plus amikacin 20) for microbiological response. The causative pathogens were not identified in 39 patients.

The comparison of patients given at least one dose of the prescribed antibiotic regimen showed no differences between the two study groups as shown in Table 2. Overall days of treatment were 10.8 (± 6.8) in the piperacillin group and 9.5 (± 8.4) in the ceftazidime group, and days of amikacin 8.1 (± 5.6) and 7.3 (± 7.4), respectively. Patients given the combination of ceftazidime and amikacin developed nosocomial pneumonia later than those given piperacillin and tazobactam plus amikacin (11.7 versus 19.9 days, $P < 0.018$). All the patients required mechanical ventilation during the treatment of the pneumonia.

The causative pathogens were identified in 50 (60.2%) of the 83 clinically evaluable patients given the combination of piperacillin/tazobactam plus amikacin, and in 20 (77%) of the 26 patients given ceftazidime plus amikacin. A total of 94 pathogens were isolated among which gram-negative bacilli predominated (52%) in both therapeutic groups (*P. aeruginosa* in 21 patients, *S. aureus* in 14, and *Haemophilus influenzae* in 14). Polymicrobial infections were diagnosed in 14 patients in the group of piperacillin/tazobactam plus amikacin and in ten patients in the ceftazidime plus amikacin group. Anaerobes were not isolated.

Clinical response at the end of treatment (Table 3) was considered satisfactory (cure or improvement) in the intention-to-treat sample in 61.4% of patients treated with piperacillin/tazobactam and in 50% of patients treated with ceftazidime (OR 1.59, 95% CI 0.73–3.47, $P = 0.244$). In the clinically evaluable population, satisfactory response was obtained in 63.9% of patients in the piperacillin/tazobactam group and in 61.5% of patients in the ceftazidime group (OR 1.1, 95% CI 0.44–2.75, $P = 0.831$).

The bacteriological response was assessed as satisfactory (eradication or presumed eradication) in 68.9% and 65.0% of both treatment groups (OR 1.19, 95% CI 0.39–3.66, $P = 0.757$) (Table 4). The eradication or presumed eradication rates corresponding to each pathogen (Table 5) responsible for the pneumonia show similar efficacy between both combinations of antibiotics with an increased eradication rate of both gram-positive (91.3 versus 78.6%) and gram-negative (82.9 versus 81.2%) bacteria. Differences in eradication rates were favorable for piperacillin/tazobactam compared to ceftazidime. Superinfections were detected in 6% of patients from the piperacillin/tazobactam group

Table 2 Baseline data and clinical course of 124 patients treated with at least one dose of the study antibiotic regimens. Data expressed as absolute number or mean (± standard deviation)

	Piperacillin/ tazobactam plus amikacin $n = 88$	Ceftazidime plus amikacin $n = 36$	P value
Sex (male, %)	64 (72.7)	26 (72.2)	0.954
Mean age (years)	57.1 ± 17	60.5 ± 20	0.342
Mean APACHE II	16.5 ± 6.6	16.9 ± 6.5	0.764
Distribution of APACHE II			0.547
0–5	5 (5.8)	1 (2.9)	
6–10	11 (12.8)	3 (8.6)	
11–15	22 (25.6)	14 (40.0)	
16–20	28 (32.6)	8 (22.9)	
> 20	20 (23.3)	9 (25.7)	
Ventilator-associated pneumonia	75 (85.2)	31 (86.1)	
Pneumonia before ICU admission	13 (14.8)	15 (13.9)	
Hospital stay before ICU admission (days)	11.7 ± 13	19.9 ± 23	0.019
Overall days of treatment	10.8 ± 6.8	9.5 ± 8.4	0.293
Days of amikacin	8.1 ± 5.6	7.3 ± 7.4	0.530
Previous antibiotics (no. patients)	43 (48.9)	21 (58.3)	
Underlying disease (%)			
Medical	55.7	58.3	
Surgical	18.2	16.7	
Injury	25.1	19.4	
Neoplasm	8	2	
Chronic bronchitis	15	7	
Diabetes	7	4	
Chronic hepatopathy	7	1	
Chronic renal failure	4	2	
Systolic blood pressure	125.3 ± 39.1	128.3 ± 37.9	
Heart rate	108.8 ± 23.2	115.3 ± 20.1	
Temperature (°C)	38.0 ± 1.2	37.7 ± 1.6	
FiO_2	0.50 ± 0.21	0.54 ± 0.21	
PEEP	5.6 ± 2.5	5.2 ± 2.6	
Leukocytes (mm^3)	13760 ± 556	16490 ± 13.9	
Neutrophils (%)	80.9 ± 9.7	79.7 ± 19.8	
Creatinine (mg%)	1.1 ± 0.6	1.0 ± 0.5	
Total protein (g/l)	5.6 ± 0.9	5.6 ± 0.8	
Crude mortality (%)	30.7	22.2	0.387
Attributed mortality	6.8	11.1	0.474

and in 15.4 % of patients from the ceftazidime group (Table 6). The analysis made in the subset of 29 patients with infections caused by *P. aeruginosa* showed similar clinical and bacteriological responses for both antibiotic regimens (Table 7).

In relation to tolerability of the study medications, a total of 21 adverse effects (23.9 %) which were possibly or probably related to antibiotics were identified among patients in the piperacillin/tazobactam group (particularly thrombocytosis and increased serum creatinine levels) as compared with only five (13.9 %) among ceftazidime-treated patients (Table 8). Adverse effects were considered severe in five patients of the piperacillin/tazobactam group and in one of the ceftazidime group. The percentage of patients with increased serum creatinine levels was similar in both arms of the study, i.e., 6.8 % ($n = 6$) in the piperacillin/tazobactam group versus 5.5 % ($n = 2$) in the ceftazidime group. None of the patients required dialysis.

The crude mortality rate was 30.7 % (27/88) in the piperacillin/tazobactam group and 22.2 % (8/36) in the ceftazidime group ($P = 0.387$). The corresponding figures for attributed mortality rate were 6.8 % (6/88) and 11 % (4/36) ($P = 0.474$). Most patients died as a result

Table 3 Efficacy of two combinations of antibiotics in patients with nosocomial pneumonia at the end of treatment. (*PP/TAZ* piperacillin/tazobactam plus amikacin, *CTZ* ceftazidime plus amikacin)

Response	Intention-to-treat		Clinically evaluable	
	PP/TAZ $n = 88$	CTZ $n = 36$	PP/TAZ $n = 83$	CTZ $n = 26$
Cure	44 (50)	16 (44)	43 (51.8)	14 (53.8)
Improvement	10 (11.4)	2 (5.6)	10 (12.1)	2 (7.7)
Failure	10 (11.4)	10 (28.8)	9 (10.8)	6 (23.1)
Relapse	3 (3.4)	0	3 (3.6)	0
Not evaluable	21 (23.9	8 (22.2)	18 (21.7)	4 (15.4)
Odds ratio (95 % CI)	1.59 (0.87–6.11)		1.1 (0.44–2.75)	
Satisfactory (cure + improvement)	54 (80.6)	18 (64.3)	53 (81.5)	16 (72.7)
Non-satisfactory (failure + relapse)	13 (14.8)	10 (28.8)	12 (18.5)	6 (27.3)
Odds ratio (95 % CI)	2.31 (0.73–3.47)		1.66 (0.54–4.12)	

Table 4 Bacteriological response in 70 cases of nosocomial pneumonia with microbiological assessment at the end of the study*

	Piperacillin/ tazobactam plus amikacin ($n = 50$)	Ceftazidime plus amikacin ($n = 20$)
Eradication	15 (30 %)	11 (55 %)
Presumed eradication	16 (32 %)	2 (10 %)
Superinfection	5 (10 %)	3 (15 %)
Relapse	2 (4 %)	1 (5 %)
Failure	7 (14 %)	3 (15 %)
Colonization	5 (10 %)	0

* OR 1.19; 95 % CI, 0.39–3.66, $P = 0.757$

of their underlying disease. Survival curves for evaluable populations in each treatment groups did not show significant differences either (Fig. 1).

Discussion

Clinical and microbiological efficacy and tolerability to the antibiotic regimen of piperacillin/tazobactam plus amikacin for treating nosocomial pneumonia in mechanically ventilated patients has been equivalent to ceftazidime plus amikacin. Both regimens were also equivalent in the subgroup of pneumonias caused by *P. aeruginosa.* However, this was an open label study and therefore the present results should be interpreted accordingly, as well as by the equivalence hypothesis set at the 20 % level. The subset of patients having non-documented pneumonia further limits the power of the

Table 5 Eradication rates of bacterial pathogens isolated in 124 patients with nosocomial pneumonia

Pathogens isolated	Piperacillin/tazobactam plus amikacin	Ceftazidime plus amikacin
Total bacteria	55/64 (85.9 %)	24/29 (82.8 %)
Gram-negative aerobic bacteria (eradicated/total)	34/41 (82.9 %)	13/16 (81.2 %)
Pseudomonas aeruginosa	8/14 (57.1 %)	5/7 (71.4 %)
Haemophilus influenzae	11/11 (100 %)	3/3 (100 %)
Escherichia coli	4/5 (80 %)	2/2 (100 %)
Serratia spp	3/3 (100 %)	1/1 (100 %)
Proteus spp	3/3 (100 %)	0/0
Acinetobacter spp	2/2 (100 %)	0/0
Enterobacter spp	2/2 (100 %)	1/2 (50 %)
Klebsiella spp	1/1 (100 %)	1/1 (100 %)
Gram-positive aerobic bacteria (eradicated/total)		
Total GP	21/23 (91.3 %)	11/14 (78.6 %)
Staphylococcus aureus	7/9 (77.8 %)	3/5 (60 %)
Streptococcus pneumoniae	6/6 (100 %)	3/3 (100 %)
Other streptococci	4/4 (100 %)	4/5 (80 %)
Enterococcus spp.	2/2 (100 %)	0/0
Other staphylococci	2/2 (100 %)	1/1 (100 %)

Table 6 Microorganisms causing superinfection

	Piperacillin/ tazobactam plus amikacin	Ceftazidime plus amikacin
Patients with superinfection	5/88 (6%)	3/36 (8.3%)
Responsible microorganisms		
Stenotrophomonas maltophilia	1	1
Escherichia coli	1	–
Klebsiella oxytoca	1	–
Pseudomonas aeruginosa	2	1
Staphylococcus aureus	–	1

Table 8 Adverse effects possibly or probably related to the antibiotic regimens

	Piperacillin/ tazobactam plus amikacin $n = 88$	Ceftazidime plus amikacin $n = 36$
Thrombocytosis	6	1
Diarrhea	3	–
Vomiting	–	1
Increased serum creatinine level	6	2
Leukopenia	1	–
Cytolysis	3	–
Hypoacusis	–	1
Cutaneous rash	1	–
Fever	1	–
Total	21 (23.9%)	5 (13.9%)

study. Patients with non-susceptible or resistant organisms were excluded from the efficacy analysis, although according to results of the intention-to-treat analysis, statistically significant differences between the study groups were not found.

Results of this study cannot be compared with previous data from studies using the combination of piperacillin and tazobactam in the management of pneumonia because of differences in the criteria used for the selection of patients, type of antibiotic regimen prescribed in the control group, and variables analyzed [21, 22, 23, 24, 25, 26] While some series [23, 24] included all nosocomial pneumonias regardless of the location and the severity of the patient's condition, other studies only analyzed the pneumonias diagnosed during the mechanical ventilation and, in this latter case, even only those in which an etiological diagnosis was obtained by invasive methods [33]. In our study, those pneumonias diagnosed in services other than the ICU that required mechanical ventilation and those diagnosed during the stay in the ICU in patients with mechanical ventilation were included. This sample of patients adapts better to the population with this infection diagnosis who are being treated in the ICU, who have the common characteristics of respiratory failure, and in whom it is necessary to know the therapeutic response of the different therapeutic proposals.

The diagnosis of pneumonia has been based on clinical and radiological criteria and only those patients in whom the therapeutic protocol was violated or in whom there were pathogens that could not be treated with the study antibiotics, whether due to the presence of resistant pathogens, to the need of alternative treatments (*Legionella* spp) or because non-bacte-

Table 7 Baseline data and clinical and microbiological response in patients with pneumonia caused by *Pseudomonas aeruginosa*

Data	Piperacillin/ tazobactam plus amikacin $n = 18$	Ceftazidime + amikacin $n = 11$	P value
Sex (men, %)	88.9	72.9	0.134
Mean age (years)	54.0 ± 19	61.8 ± 20	0.306
Mean APACHE II	14.8 ± 6.0	17.9 ± 8.1	0.224
Previous stay (days)	19.3 ± 19	20.6 ± 26	0.982
Days of treatment	12.5 ± 8.4	11.4 ± 11.8	0.649
Days on amikacin	8.22 ± 5.2	6.6 ± 6.5	0.457
Baseline disease			0.072
Medical	33.3	63.6	
Surgical	44.4	18.2	
Traumatic	22.2	18.2	
Satisfactory clinical response (cure + improvement)			
Intention-to-treat population	12/18 (66.7%)	6/11 (54.5%)	0.514
Clinically evaluable population[a]	12/14 (85.7%)	6/7 (85.7%)	1.000
Satisfactory microbiological response (eradication + presumed eradication)			
Intention-to-treat population	8/18 (44.4%)	5/11 (45.4%)	0.958
Clinically evaluable population[a]	8/14 (57.1%)	5/7 (71.4%)	0.525

[a] Four patients in each group were excluded, piperacillin/tazobactam group (protocol violation 1, resistance to other associated pathogen 3); ceftazidime group (protocol violation 1, resistant *P. aeruginosa* 2, resistance to another associated pathogen 1)

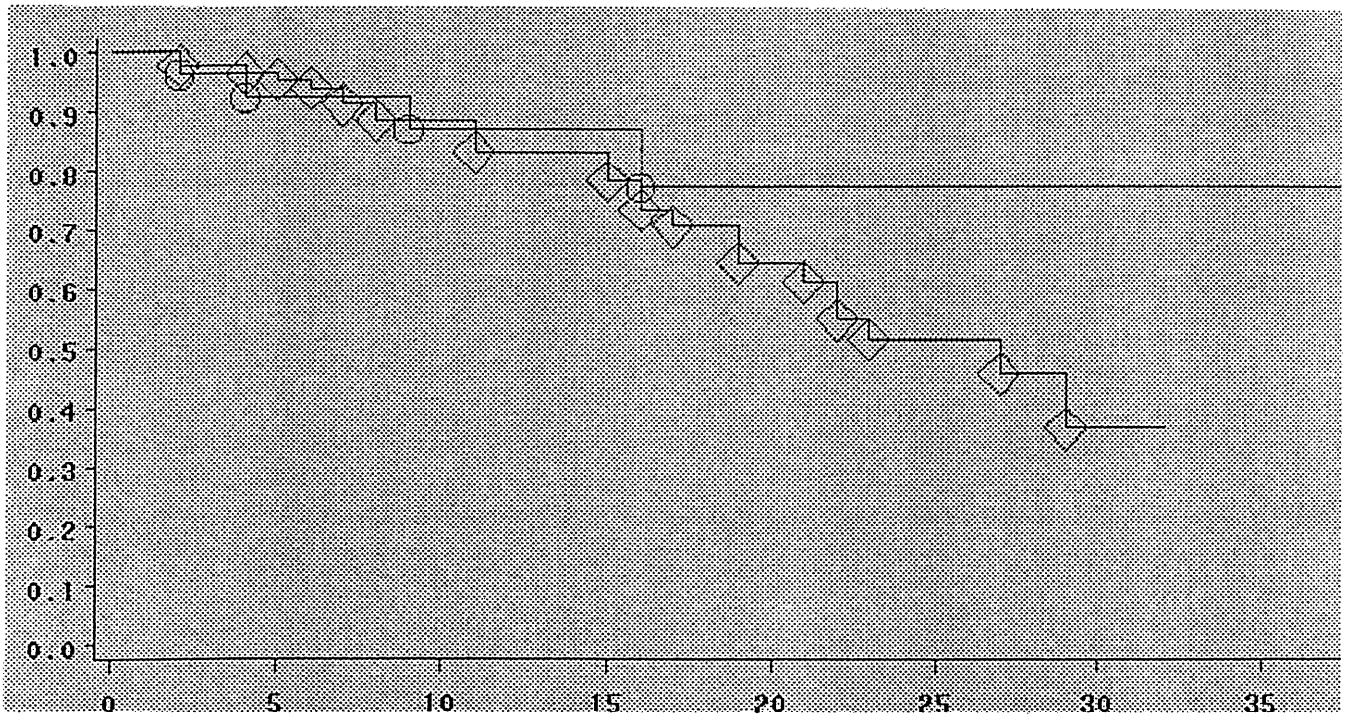

Fig. 1 Comparison of Kaplan-Meier survival curves for patients treated with piperacillin/tazobactam and amikacin *(open diamonds)* and patients treated with ceftazidime and amikacin *(open circles)* (*x* axis = time on treatment; *y* axis = survival distribution function)

rial pathogens (*Aspergillus* spp) were observed, were excluded from the study. In the ceftazidime plus amikacin group, 27.8% of the randomized patients were excluded for these reasons while only 5.7% from the piperacillin/tazobactam group were excluded. In other studies [33], those patients for whom an etiological diagnosis was not obtained were excluded, this being an important bias since this infectious disease is not diagnosed in 20–40% of the patients. In our study, the pathogenic agents were only identified in 64.2% of the patients.

Recently, the importance of using adequate empirical treatment from the first moment when the diagnosis of nosocomial pneumonia is suspected has been documented [34]. The use of inadequate empirical antibiotics (to which the pathogenic agents of the infection were resistant) has been associated with increased morbidity and mortality and, in general, with poor prognosis [35, 36, 37]. In our study, the presence of resistant pathogens was the reason for exclusion in six of 36 ceftazidime-treated patients (*P. aeruginosa, Enterococcus* spp, *S. aureus*, *S. marcescens*) as compared with only two of 88 patients in the piperacillin/tazobactam group *(S. aureus, Acinetobacter baumannii)*.

The pathogens most frequently recovered were *P. aeruginosa* followed by methicillin-susceptible *S. aureus* and *H. influenzae*. These microorganisms are the most frequent in the majority of mechanically ventilated patients with nosocomial pneumonia, especially in a polymicrobial form [3, 4, 5, 6, 7, 8]. The eradication rate for each one of them was greater than 80% in each therapeutic group, except for *P. aeruginosa* which reached rates of 57.1% and 71.4% for the piperacillin/tazobactam and ceftazidime groups, respectively, even though the clinical efficacy was similar in both arms. These eradication rates were greater than those found by others in studies using ciprofloxacin or imipenem as monotherapies [38].

Recently, the use of monotherapy has been proposed for the treatment of these infections using wide-spectrum antibiotics, such as imipenem/cilastatin, ciprofloxacin or meropenem [38, 39, 40, 41, 42], although there are no prospective and comparative studies which analyze their efficacy in monotherapy compared to treatment combined with aminoglycosides. However, the high frequency of pneumonias caused by *P. aeruginosa* in this group of patients which has been associated in some studies with greater failure, recurrence and/or appearance of resistance rates during treatment, advise against their empirical use [38, 39, 40, 41, 42, 43]. Combined treatment in our experience was accompanied by an elevated rate of clinical and microbiological efficacy and was associated with a low rate of superinfections (10% and 20%, respectively) in which gram-negative bacilli (*P. aeruginosa*, *Stenotrophomona maltophilia,* and others) were basically involved.

The use of both combinations was equally effective in the treatment of *P. aeruginosa*-produced pneumonias, although the population in whom the analysis was performed is reduced. The maximum doses recommended for the treatment of non-fermenting gram-negative bacilli pneumonia were used in both therapeutic arms, although plasma levels were not measured in order to assure the presence of serum concentrations of the antibiotics used superior to the minimum inhibitory concentration (MIC) of this bacteria. The analysis of the characteristics of both populations with *P. aeruginosa* demonstrates that there were no significant differences between them, so that piperacillin/tazobactam plus amilkacin is as useful as the reference regimen of ceftazidime plus amikacin.

In our study, like others, no case of anaerobic infection was diagnosed, although procedures for obtaining pulmonary samples and microbiologic processing are not adequate for the isolation of anaerobic bacteria. However, the lack of differences in the clinical response between both antibiotic combinations to one of which anaerobes are susceptible, suggests the low relevance of these pathogens in the etiology of nosocomial pneumonia.

Both combinations have been well tolerated and most of the severe adverse effects were related to an increase in serum creatinine level, which was probably or possibly due to the use of aminoglycosides. Although these are seriously ill patients in whom there may be more than one factor contributing to the renal lesion, our data suggest that the use of nephrotoxic antibiotics in combination with β-lactam antibiotics should be monitored by determination of plasma concentrations of aminoglycosides every 2–3 days and daily assessment of the renal function. Although in six patients in the piperacillin/tazobactam group a moderate increase in the number of platelets was detected, withdrawal of treatment for this reason was not required.

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