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Prospective Randomized Comparison of Imipenem-Cilastatin and Piperacillin-Tazobactam in Nosocomial Pneumonia or Peritonitis

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Nosocomial pneumonia and acute peritonitis may be caused by a wide array of pathogens, and combination therapy is often recommended. We have previously shown that imipenem-cilastatin monotherapy was as efficacious as the combination of imipenem-cilastatin plus netilmicin in these two settings. The efficacy of imipenem-cilastatin is now compared to that of piperacillin-tazobactam as monotherapy in patients with nosocomial pneumonia or acute peritonitis. Three hundred seventy one patients with nosocomial pneumonia or peritonitis were randomly assigned to receive either imipenem-cilastatin (0.5 g four times a day) or piperacillin-tazobactam (4.5 g three times a day). Three hundred thirteen were assessable (154 with nosocomial pneumonia and 159 with peritonitis). For nosocomial pneumonia, clinical-failure rates in the piperacillin-tazobactam group (13 of 75 [17%]) and in the imipenem-cilastatin group (23 of 79 [29%]) were similar ($P = 0.09$), as were the numbers of deaths due to infection (6 in the imipenem-cilastatin group [8%], 7 in the piperacillin-tazobactam group [9%]) ($P = 0.78$). For acute peritonitis, clinical success rates were comparable (piperacillin-tazobactam, 72 of 76 [95%]; imipenem-cilastatin, 77 of 83 [93%]). For infections due to *Pseudomonas aeruginosa*, 45 patients had nosocomial pneumonia (21 in the piperacillin-tazobactam group and 24 in the imipenem-cilastatin group) and 10 had peritonitis (5 in each group). In the patients with nosocomial pneumonia, clinical failure was less frequent in the piperacillin-tazobactam group (2 of 21 [10%]) than in the piperacillin-cilastatin group (12 of 24 [50%]) ($P = 0.004$). Bacterial resistance to allocated regimen was the main cause of clinical failure (1 in the piperacillin-tazobactam group and 12 in the imipenem-cilastatin group). For the patients with peritonitis, no difference in clinical outcome was observed (five of five cured in each group). The overall frequencies of adverse events related to treatment in the two groups were similar (24 in the piperacillin-tazobactam group, 22 in the imipenem-cilastatin group). Diarrhea was significantly more frequent in the piperacillin-tazobactam group (10 of 24) than in the imipenem-cilastatin group (2 of 22). This study suggests that piperacillin-tazobactam monotherapy is at least as effective and safe as imipenem-cilastatin monotherapy in the treatment of nosocomial pneumonia or peritonitis. In *P. aeruginosa* pneumonia, piperacillin-tazobactam achieved a better clinical efficacy than imipenem-cilastatin, due to reduced development of microbiological resistance. Tolerance was comparable, with the exception of diarrhea, which was more frequent with piperacillin-tazobactam.

Pneumonia is the second most common type of nosocomial infection (3, 14, 15, 18). It represents 15 to 18% of nosocomial infections, translating into four to seven episodes/1,000 hospitalizations (0.6 to 1.1% of hospitalized patients or 10 to 25% of patients in intensive care units [ICU]) (13, 14). In ventilated patients, the rate of nosocomial pneumonia in medical and surgical ICU is 15/1,000 ventilator days and is increased 4- to 21-fold in comparison with nonintubated ICU patients (14). Furthermore, nosocomial pneumonia is, besides bloodstream infection, the leading cause of death from hospital-acquired infections (4, 13, 20) and also increases significantly survivors' length of stay (13, 14). It can be caused by a wide array of pathogens including aerobic and anaerobic gram-negative and gram-positive bacteria (3, 14, 15, 29, 45). As the responsible pathogens are usually not known at the time of presentation and early and effective antibiotic therapy is correlated to survival (3, 30, 45), empirical broad-spectrum antibiotic coverage is initially recommended, either in monotherapy or in combination therapy (3, 14, 15, 30, 45).

Secondary peritonitis is another clinical setting which requires the empiric administration of antibiotics. Since this infection is usually due to polymicrobial flora, a broad coverage including anaerobes and *Enterobacteriaceae* is needed, as shown by Bartlett's observation more than 25 years ago (2). Since then, a combination of clindamycin or metronidazole with an aminoglycoside has been considered standard therapy for peritonitis (17, 39). However, the development of carbapenems, broad-spectrum cephalosporins, or fluoroquinolones has afforded the possibility of restraining the use of aminoglycosides which are associated with potential nephrotoxicity and ototoxicity. Despite numerous methodological problems in several trials using patients with peritonitis, monotherapy appeared as effective as standard combinations in this setting (10, 23, 24, 32). Indeed, in a well-designed study, Solomkin et al. showed that imipenem-cilastatin was even more effective than a com-

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bination of clindamycin and tobramycin in patients with secondary peritonitis (41).

Piperacillin is a semisynthetic ureidopenicillin with a broad spectrum of activity against gram-positive and gram-negative aerobic and anaerobic bacteria and with an improved activity against *Pseudomonas aeruginosa* compared with other ureidopenicillins (6). This expanded-spectrum penicillin is nevertheless susceptible to hydrolysis by several β-lactamases (1). Tazobactam, an inhibitor derived from penicillic acid sulfone, inhibits a wide range of commonly encountered β-lactamases of the chromosomal and plasmid-mediated types (1, 6). The combination of piperacillin and tazobactam is active in vitro against a large spectrum of bacteria including *Enterobacteriaceae*, *Pseudomonas*, anaerobes, and staphylococci (1, 6). Comparative and noncomparative clinical studies with or without an aminoglycoside have been conducted with patients with intra-abdominal infections (5, 23, 31, 32, 35), complicated urinary tract infections (34), bacteremia (7), bone and joint infections (6), gynecological infections (6, 43), empiric treatment of febrile neutropenia (11, 12, 16), and community-acquired or nosocomial pneumonia (29, 37). In all these studies, piperacillin-tazobactam has shown either a similar or a better efficacy than the comparative regimen (34, 37, 38). There was also a paucity of data comparing piperacillin-tazobactam monotherapy to other regimens in the treatment of nosocomial pneumonia. Therefore, the present study was conducted to assess the efficacy and safety of piperacillin-tazobactam in comparison to those of imipenem-cilastatin in the treatment of nosocomial pneumonia or peritonitis.

MATERIALS AND METHODS

Study design. The study was conducted from December 1993 to May 1996 in the medical and surgical wards and ICU of three Swiss hospitals: Geneva University Hospital (206 randomized patients), Lausanne University Hospital (142 randomized patients), and Sion Regional Hospital (23 randomized patients). This prospective randomized controlled trial was approved by the human-research ethics committee of each participating center. In each center, consecutive patients who fulfilled the inclusion criteria were randomly assigned to one of the two treatment regimens by sealed numbered envelopes. The randomization was stratified according to type of infection (pneumonia or peritonitis). Each study center had its own block numbers for randomization.

Criteria for eligibility. Patients were eligible if they were more than 16 years old and had given informed consent.

(i) Nosocomial pneumonia. Nosocomial pneumonia was diagnosed as a new infiltrate on chest X ray 72 h or more after admission with two or more of the following symptoms: fever ≥38°C, new onset of production of purulent sputum, significant increase in volume of purulent sputum, or peripheral leukocyte (WBC) count $>10^{10}$/liter (22). Microbiological diagnosis was attempted in all cases prior to inclusion and included cultures of sputum, nasotracheal aspirate, aspirate through orotracheal tube, bronchoscopy with bronchoalveolar lavage (BAL) and/or protected brush specimens, pleural fluid, and blood. Pneumonia was microbiologically documented if cultures of sputum or tracheal aspirate showed one or more predominant pathogens and microscopical examination showed more than 25 polymorphonuclear cells and fewer than 10 epithelial cells per low-power (×100) field (22). For BAL and protected brush specimens, we used cutoff values of 10^4 and 10^3 CFU/ml, respectively, as previously (8).

(ii) Acute peritonitis. Acute peritonitis was assessed intraoperatively, and microbiological documentation was attempted in all cases. The only exception was sigmoid diverticulitis, which was defined as muscle guarding and rebound tenderness in the left iliac fossa or left flank with leukocytosis (WBC count, $>10^{10}$/liter) or leukopenia (WBC count, $<4 \times 10^9$/liter) and fever ≥38°C. In cases where a computerized axial tomography scan was diagnostic, peritonism in left lower quadrant was sufficient for inclusion.

(iii) Exclusion criteria. Exclusion criteria included pregnancy or lactating state, expected survival of less than 48 h, known allergy to β-lactam antibiotics or β-lactamase inhibitors, human immunodeficiency virus infection, concomitant infection other than intra-abdominal or nosocomial pneumonia, infection with microorganisms known to be resistant to either of the study treatments, previous treatment with any appropriate antibacterial agent for the same infection, previous inclusion in the trial, and finally, serum transaminase, alkaline phosphatase, and bilirubin levels greater than or equal to three times the upper normal limit.

Treatment. Patients were openly assigned to one of the following two regimens: piperacillin-tazobactam at 4.5 g three times a day or imipenem-cilastatin at 500 mg four times a day. The dosage of each regimen was adjusted to renal function.

Collection of data. A complete history and a physical examination were performed for each patient at baseline. At each center, all patients were monitored each day by a local investigator. Clinical data was recorded on each day of treatment: vital signs, adverse events, concomitant medication, any modification of study drug dosage; for patients with nosocomial pneumonia, description of respiratory secretion, sputum production, severity of cough, rales on auscultation or dullness on percussion, mechanical ventilation, FiO_2, pO_2, PEEP; for patients with peritonitis, oral fluid intake, diet, nausea and/or vomiting, abdominal pain, peritonism on physical examination, qualitative aspect of drainage, fluid bowel sounds, healing of surgical wound. Blood chemistry and hematology were performed at baseline, on day 3, within two days posttreatment (early follow-up), and between 2 and 4 weeks posttreatment if appropriate (late follow-up). Microbiological samples were taken at baseline, on day 3, and on early and late follow-ups if appropriate and included blood cultures and cultures from respiratory, abdominal, or any other relevant clinical focus of infection.

Clinical efficacy was assessed according to published clinical guidelines (9, 42) at the end of treatment and 2 to 4 weeks after the end of treatment by a follow-up interview.

Peritonitis. Patients with peritonitis were considered to have been clinically cured if the initial course of therapy and the initial intervention resolved the intra-abdominal infectious process. Any further antibiotic treatment or surgery for peritonitis within 7 days after the end of treatment was considered a failure of the original treatment (42).

Nosocomial pneumonia. For patients with nosocomial pneumonia, cure was defined as the complete resolution of all signs and symptoms of pneumonia and improvement or lack of progression of all abnormalities on chest radiograph. As with peritonitis, any further antibiotic therapy for pneumonia within 7 days after the end of therapy was considered to render the original treatment a failure (9).

In both nosocomial pneumonia and peritonitis, failure was defined as either persistence or progression of signs and symptoms of infection (no clinical improvement), lack of improvement associated with a pathogen resistant to the allocated regimen, development of a breakthrough bacteremia or sepsis, or relapse. Patients who were not cured according to the above defined criteria were also categorized under "failure."

A study coordinator (C.J.) discussed all patients with the local investigators and entered the data in the database with the help of a research nurse (D.A.). In addition, all patients with a diagnostic problem or a complicated clinical course as well as patients who failed therapy or were not evaluable were assessed by a blinded investigator (A.C.).

Microbiological susceptibility tests. Antimicrobial susceptibility tests were done by agar disc diffusion according to National Committee for Clinical Laboratory Standards guidelines. Any isolate with an inhibition zone ≤17 mm in diameter for piperacillin-tazobactam and ≤13 mm for imipenem was considered resistant to the antibiotic.

Statistical analysis. Statistics were run with the SAS software package (SAS Institute Inc., Cary, N.C.). All tests were two-tailed. A P value ≤0.05 was considered significant.

Proportions and means in baseline characteristics and outcome were compared between treatments by using Fisher's exact test, two-sample t test with pooled variance, or Wilcoxon test, as appropriate. In considering outcomes, relative risks (RRs) with 95% confidence intervals (95% CIs) were used to measure the size of the effect of the tested regimen (piperacillin-tazobactam) versus the reference regimen (imipenem-cilastatin).

Adjusted analyses were run when necessary. The Mantel-Haenszel stratified test was used to measure adjusted relative risks for an outcome while controlling for a potential confounding factor with a binomial distribution. Multivariate logistic regression was used to get adjusted odds ratios when several potential confounding factors were identified for a group or subgroup, whether they were discrete or continuous.

RESULTS

Three hundred seventy-one patients were randomized, of whom 58 were not evaluable for response because of violation of entry criteria (37 patients), less than 48 h of therapy (13 patients), addition of another antibiotic without adequate reason (4 patients), early stop of resuscitation (3 patients), or early toxicity (1 patient). Twenty-two of these patients were receiving imipenem-cilastatin, and 36 were receiving piperacillin-tazobactam. Among the 313 remaining patients, 154 had nosocomial pneumonia and 159 had acute peritonitis.

Nosocomial pneumonia. Among the 154 evaluable patients in the pneumonia group, 75 received piperacillin-tazobactam and 79 received imipenem-cilastatin. Baseline characteristics were equally distributed between the two treatments, with the exception of bacteremic infections, which were more common

TABLE 1. Patient characteristics at baseline[a]

Characteristic	Value for group	
	Piperacillin-tazobactam (%)	Imipenem-cilastatin (%)
Nosocomial pneumonia		
Total	75	79
Age (yr)	56.6 ± 17.6	59.7 ± 16.9
Wt (kg)	71.4 ± 15.4	70.1 ± 17.3
APACHE II at randomization	14.6 ± 6.8	14.9 ± 6.8
Male/female	58/17	52/27
No. of comorbidities:		
0	1 (1.3)	1 (1.3)
1–2	35 (46.7)	29 (36.7)
3–4	30 (40.0)	31 (39.2)
>4	9 (12.0)	18 (22.8)
Mechanical ventilation	35 (47)	40 (51)
PEEP	6.4 ± 2.2	6.2 ± 2.4
pO_2/FiO_2	143.7 ± 75.3	140.3 ± 64.2
Antibiotics before randomization	47 (63)	47 (59)
Previous surgery	57 (76)	57 (72)
Bacteremia	3 (4)	10 (13)*
Peritonitis		
Total	76	83
Age (yr)	59.1 ± 20.4	59.1 ± 18.5
Wt (kg)	68.4 ± 13.9	69.9 ± 14.3
APACHE II at randomization	8.3 ± 6.3	7.3 ± 4.9
Male/female	36/40	50/33
No. of comorbidities:		
0	22 (29)	28 (34)
1–2	35 (46)	35 (42)
3–4	15 (20)	18 (22)
>4	4 (5)	2 (2)
Antibiotics before randomization	7 (9)	2 (2)
Mechanical ventilation	4 (5)	5 (6)
Bacteremia	7 (9)	10 (12)
Causes of peritonitis		
Unperforated acute appendicitis	9	14
Acute cholecystitis	3	1
Unperforated acute diverticulitis	10	19
Perforation in the upper GI[b] tract	20	12
Perforation in the large bowel	26	31
Other cause	8	6

[a] No significant differences between the two groups were found by two-tailed Fisher's exact test for binomial variables (sex, mechanical ventilation, antibiotics before randomization) and two-sample *t* test with pooled variance for continuous variables (age, weight, APACHE II). *, $0.05 < P < 0.10$.
[b] GI, gastrointestinal.

in the imipenem-cilastatin group (10 of 79 versus 3 of 75 [$P = 0.08$]) (Table 1).

Nosocomial pneumonia was microbiologically documented in 124 of 154 patients (81%), 58 of 75 (77%) in the piperacillin-tazobactam group and 66 of 79 (83%) in the imipenem-cilastatin group ($P = 0.42$) (Table 2). The samples leading to microbiological diagnosis were (i) sputum or tracheal aspirate (41 for piperacillin-tazobactam versus 43 for imipenem-cilastatin), (ii) BAL or protected brush (14 versus 13), and (iii) blood (3 versus 10) (Table 2). In 60% (75 of 124) of cases of microbiologically documented pneumonia, a unique pathogen was recovered. In this subgroup, gram-negative bacilli were predominant (63 of 75 [84%]) and *P. aeruginosa* was the most frequently isolated pathogen (28 of 63 [44%]). *Staphylococcus aureus* and *Streptococcus pneumoniae* were the only two gram-positive organisms isolated in the monobacterial pneumonia subgroup and represented together only 16% (12 of 75). Mixed infections were observed in 40% of microbiologically documented cases of pneumonia (49 of 124). Again, in this subgroup *P. aeruginosa* was the most frequently found pathogen (isolated in 17 of 49 patients [35%]) (Table 2).

Thirteen patients on piperacillin-tazobactam (17%) and 23 on imipenem-cilastatin (29%) experienced a clinical failure, a difference which was not statistically significant (RR = 0.6; $P = 0.09$) (Table 3). Seven patients receiving piperacillin-tazobactam (9%) and six patients receiving imipenem-cilastatin (8%) died from infection (RR = 1.23, $P = 0.78$). Since patients treated with imipenem-cilastatin were more often bacteremic than patients with piperacillin-tazobactam and since this could act as a confounding factor (44), a stratified analysis was performed. Although the adjusted RRs obtained from this analysis (piperacillin-tazobactam versus imipenem-cilastatin) were 0.63 for clinical failure and 1.41 for death due to infection, the 95% CIs for these two RRs still included 1.0, allowing for the possibility of no difference between the two treatments, thus confirming the results of the crude analysis.

Acute peritonitis. Among the 159 evaluable patients with peritonitis, 76 were randomized to the piperacillin-tazobactam group and 83 were randomized to the imipenem-cilastatin group. Baseline characteristics of these patients were well balanced between the two groups and are listed in Table 1.

Peritonitis was microbiologically documented for 88 of 159 patients (55%); 65 of the 88 cases were polymicrobial. The pathogens isolated were mainly gram-negative bacteria (102 isolates) including *Enterobacteriacae*, *P. aeruginosa*, *Citrobacter* sp., *Haemophilus influenzae*, and gram-positive cocci (59 isolates) including enterococci, *Streptococcus* sp., *S. aureus*, and anaerobes (60 isolates). Surgery was performed for 130 of the 159 patients; those that were not operated on were patients with unperforated diverticulitis.

In the treatment of peritonitis (Table 3), piperacillin-tazobactam was clinically successful in 72 of 76 patients (95%) and imipenem-cilastatin was clinically successful in 77 of 83 (93%) (RR = 1.02; $P = 0.75$). There were no significant differences in mean duration of treatment or death due to infection.

TABLE 2. Documentation and microbiology of nosocomial pneumonia

Characteristic	No. of patients	
	Piperacillin-tazobactam ($n = 75$) [%]	Imipenem-cilastatin ($n = 79$) [%]
Clinical documentation	17 [23]	13 [17]
Microbiological documentation	58 [77]	66 [83]
Sputum	18	17
Tracheal aspirate	23	26
BAL	11	8
Protected brush	3	5
Blood	3	10
Gram-negative bacteria	29	34
P. aeruginosa	16	12
E. coli	2	5
Enterobacter sp.	2	4
Klebsiella sp.	2	2
H. influenzae	2	2
Other	5	9
Gram-positive bacteria	4	8
S. pneumoniae	2	4
S. aureus	2	4
Mixed	25	24
P. aeruginosa + other	5	12

TABLE 3. Outcomes in patients according to type of infection

Characteristic	No. of patients		RR [95% CI]	P^a
	Piperacillin-tazobactam (%)	Imipenem-cilastatin (%)		
Nosocomial pneumonia				
Total	75	79		
Success	62 (83)	56 (71)	1.17 [0.98–1.39]	0.09
Failure	13 (17)	23 (29)	0.60 [0.33–1.09]	0.09
Resistance to allocated regimen and no clinical improvement	4	7		
No clinical improvement	5	5		
Breakthrough bacteremia	2	4		
Septic shock or MOF[b]	1	4		
Relapse	1	3		
Death due to infection	7 (9.3)	6 (7.6)	1.23 [0.43–3.49]	0.78
Mean duration of treatment ± SD	9.4 ± 4.3	9.9 ± 4.6		0.45
Peritonitis				
Total	76	83		
Success	72 (95)	77 (93)	1.02 [0.94–1.11]	0.75
Failure	4 (5)	6 (7)	0.73 [0.21–2.48]	0.75
Further infection	2	1		
No clinical improvement	1	0		
Resistance to allocated regimen	0	1		
Relapse	1	3		
Septic shock or MOF	0	1		
Death due to infection	1 (1.3)	2 (2.4)	0.55 [0.05–5.9]	1.00
Mean duration of treatment ± SD	8.2 ± 2.8	8.5 ± 3.3		0.53

[a] Two-tailed Fisher's exact test for binomial variables (death due to infection, success, failure); two-sample *t* test with pooled variance for continuous variables (duration of treatment).
[b] MOF, multiple organ failure.

Infections due to *P. aeruginosa*. Since pneumonia due to *P. aeruginosa* is associated with a worse prognosis (4, 17–20, 25, 36, 42), a subgroup analysis was done on the 55 patients with infections due to *P. aeruginosa* (Table 4). Forty-five patients had nosocomial pneumonia (21 were treated with piperacillin-tazobactam and 24 were treated with imipenem-cilastatin); 10 had peritonitis (5 in each group). The baseline characteristics of the patients with nosocomial pneumonia were different in terms of sex (male/female ratio, 16/5 in the piperacillin-tazobactam group versus 11/13 in the imipenem-cilastatin group [$P = 0.07$]), number of polymicrobial infections (piperacillin-tazobactam, 5 of 21; imipenem-cilastatin, 13 of 24 [$P = 0.07$]), and APACHE II score (piperacillin-tazobactam, 10.9; imipenem-cilastatin, 14.3 [$P = 0.06$]). Clinical failures were observed more often in patients treated with imipenem-cilastatin (12 of 24 [50%]) than in patients treated with piperacillin-tazobactam (2 of 21 [10%]) ($P = 0.004$). They were mainly due to the development of resistance (six to imipenem-cilastatin, one to piperacillin-tazobactam) or initial resistance (one to imipenem-cilastatin, none to piperacillin-tazobactam) to the allocated regimen. In a crude analysis, the RR for clinical failure comparing piperacillin-tazobactam to imipenem-cilastatin was 0.19 (95% CI, 0.05 to 0.76) ($P = 0.004$) (Table 4). A multivariate logistic regression model was built to control for

TABLE 4. Outcomes of infections due to *P. aeruginosa* (alone or in combination with other organisms) according to treatment regimen

Characteristic	No. of patients (%)		RR [95% CI]	P^a
	Piperacilliin-tazobactam	Imipenem-cilastatin		
Nosocomial pneumonia				
Success	19/21 (90.5)	12/24 (50)	1.81 [1.18–2.76]	0.004
Failure[b]	2/21 (9.5)	12/24 (50)	0.19 [0.05–0.76]	0.004
Resistance + no clinical improvement	1	7		
Breakthrough bacteremia	0	1		
Relapse	0	1		
Further infection	1	0		
No improvement	0	1		
Septic shock or MOF[c]	0	2		
Acute peritonitis				
Success	5/5 (100)	5/5 (100)	1	
Failure	0/5	0/5	1	

[a] Two-tailed Fisher's exact test.
[b] *P. aeruginosa* becoming resistant to the allocated regimen: piperacillin-tazobactam group, 1 patient; imipenem-cilastatin group, 6 patients. Initially, there were no cases of resistance in the piperacillin-tazobactam group and one case of resistance in the imipenem-cilastatin group.
[c] MOF, multiple organ failure.

APACHE II score, polymicrobial infections, and sex ratio. It confirmed that clinical failure was significantly more frequent in the imipenem-cilastatin group than in the piperacillin-tazobactam group (odds ratio, 0.10; 95% CI, 0.01 to 0.66). However, there was no difference in mortality due to infection.

In the 10 patients (5 in each group) with peritonitis and documentation of *P. aeruginosa*, the clinical outcomes were similar (all were cured).

Adverse events related to treatment. Adverse events probably or definitely related to study drug (namely, cutaneous allergic reaction, *Candida albicans* infection, *Clostridium difficile* colitis, nephrotoxicity, hepatotoxicity, hematotoxicity, and colonization by a resistant organism) did not differ between the two groups (24 in the piperacillin-tazobactam group and 22 in the imipenem-cilastatin group). However, diarrhea was significantly more frequent in patients treated with piperacillin-tazobactam than in patients treated with imipenem-cilastatin (10 of 151 versus 2 of 162 [$P = 0.002$ by two-tailed Fisher's exact test]). One seizure was observed in the imipenem-cilastatin group, and none was observed in the piperacillin-tazobactam group. There was no difference in the occurrence of further infections between the two groups.

DISCUSSION

With the advent of broad-spectrum bactericidal antibiotics, the need for antibiotic combinations including aminoglycosides for the treatment of severe infections has been challenged in various infections over the last 10 years. For febrile patients with long-lasting neutropenia, recent data shows that monotherapy with carbapenem or broad-spectrum cephalosporins was as effective as combination therapy with β-lactam antibiotics and aminoglycosides (10, 16). For patients with nosocomial pneumonia, monotherapy with broad-spectrum antibiotics has proven to be a useful alternative to combination therapy (26–28, 39). In a previous study (10) performed mainly with patients with nosocomial pneumonia or peritonitis, we have shown that monotherapy with imipenem-cilastatin was as efficacious as a combination of imipenem-cilastatin and netilmicin, thus demonstrating that broad-spectrum antibiotics such as carbapenems might be sufficient and a combination with an aminoglycoside does not improve outcome. In addition, the drawback of combination therapies with aminoglycosides is toxicity, especially in critically ill patients. This was confirmed in the trial of imipenem-cilastatin versus imipenem-cilastatin plus netilmicin which showed an increased nephrotoxicity in patients given the combination therapy (10). Several other trials have compared monotherapy to combination therapy for the treatment of nosocomial pneumonia (10, 26–28, 40) or peritonitis (35, 41, 42) and have shown the monotherapy to have either a similar or a better efficacy. The present study shows that piperacillin-tazobactam is an efficacious and safe alternative to imipenem-cilastatin in the treatment of nosocomial pneumonia and peritonitis. Indeed, regarding efficacy in patients with nosocomial pneumonia, the success rate with piperacillin-tazobactam (83%) is similar to that observed in other studies assessing the treatment of nosocomial pneumonia with either monotherapy or combination therapy (10, 26–28, 40). In the present study, the causes for failure and the numbers of deaths due to infection did not differ between the two groups. Although the difference in success rate between the two groups was not statistically significant, there was a trend in favor of piperacillin-tazobactam. Therefore, we cannot exclude the possibility that statistical significance could have been reached with a larger sample size. However, this data suggests that piperacillin-tazobactam monotherapy is at least as effective as imipenem-cilastatin, which is commonly used in the treatment of nosocomial pneumonia and peritonitis.

Despite randomization, the two groups were somewhat imbalanced regarding bacteremia at baseline. Since this parameter is negatively related to prognosis (3, 14, 44), a stratified analysis was run to adjust for this potential confounding factor. The result confirmed the equivalence of the two treatments regarding clinical efficacy. Although analysis of subgroups may be questionable for methodological reasons because the benefit of randomization may be lost, we believe that those results are worth presenting. Indeed, potential confounding factors were first identified in the subgroup of patients with pneumonia due to *P. aeruginosa*, and an adjusted analysis (logistic regression) was run, confirming the crude analysis.

The emergence of *P. aeruginosa* resistant to imipenem-cilastatin has been reported in several trials. The development of resistance to imipenem-cilastatin in *P. aeruginosa* is related to the loss of a specific porin (OpR2). Our previous study showed that imipenem-cilastatin resistance was not prevented by the addition of netilmicin (10). In two studies comparing imipenem-cilastatin to either ceftazidime (33) or ciprofloxacin (21), imipenem-cilastatin was less effective than ceftazidime or ciprofloxacin in the *P. aeruginosa* pneumonia subgroup. In both studies, the development of resistance to imipenem-cilastatin in *P. aeruginosa* strains explained the lower efficacy of imipenem-cilastatin. We now report that piperacillin-tazobactam is superior to imipenem-cilastatin in preventing the emergence of *P. aeruginosa* resistance. Piperacillin is highly active against *P. aeruginosa* (1, 6, 38). When piperacillin resistance develops in *P. aeruginosa*, it is mostly due to a chromosomal β-lactamase. Tazobactam is active against Richmond and Sykes class II to V β-lactamases and against extended-spectrum β-lactamases but has only species-specific activity against chromosomal class Ic β-lactamases. In particular, tazobactam is usually not active against *P. aeruginosa* chromosomal β-lactamases and thus does not reverse piperacillin resistance in *P. aeruginosa* strains resistant to piperacillin. On the other hand, tazobactam has no inducing capacities on chromosomal class I β-lactamases (6) and therefore exerts only a minimal selective pressure in favor of species producing this class of β-lactamase. Thus, it is clear that the improved efficacy of piperacillin-tazobactam over that of imipenem-cilastatin for *P. aeruginosa* pneumonia can be expected only in clinical centers in which *P. aeruginosa* resistance to piperacillin is low, as is the case in the three centers involved in the present study.

In acute peritonitis, piperacillin-tazobactam was equivalent to imipenem-cilastatin in our study. Both drugs achieved excellent cure rates, in excess of 90% (95 and 93%, respectively). The clinical cure rate for piperacillin-tazobactam was comparable to that (91%) in the study by Brismar et al. which also compared piperacillin-tazobactam to imipenem-cilastatin in intra-abdominal infections (5). However, while the clinical cure for imipenem-cilastatin was only 69% in the latter study, it reached 93% in our study. This improved efficacy of imipenem-cilastatin for peritonitis was probably related to the daily dosage of imipenem-cilastatin used in the present study (0.5 g four times a day instead of three times a day in the study by Brismar et al.). In the study by Brismar et al. most of the difference in clinical failures between the two groups was due to more frequent development of intra-abdominal abscesses and surgical-wound infection in the imipenem-cilastatin group. In the present study we observed equal distributions of clinical failures in the two treatment groups, i.e., only one case of intra-abdominal abscess in the piperacillin-tazobactam group and none in the imipenem-cilastatin group, while surgical-wound infections were equally distributed between the two treatment

groups. Most importantly, the present study confirms previous trials demonstrating that a combination treatment with aminoglycoside in intra-abdominal infections can be replaced by less toxic monotherapies.

Both treatments were well tolerated, with comparable amounts of adverse reactions, with the exception of diarrhea, which was more frequent in the piperacillin-tazobactam-treated patients. It is worth noting that this difference had already been observed in a study comparing piperacillin-tazobactam to clindamycin and gentamicin in women with pelvic infections, where diarrhea was significantly more frequent in patients treated with piperacillin-tazobactam (43).

In conclusion, piperacillin-tazobactam monotherapy is at least as effective and safe as imipenem-cilastatin in the treatment of nosocomial pneumonia and peritonitis. In *P. aeruginosa* nosocomial pneumonia, piperacillin-tazobactam was associated with an improved efficacy over that of imipenem-cilastatin. The observed failures were mainly due the development of microbiological resistance to imipenem-cilastatin. Finally, adverse events and superinfections were equally distributed between the two treatment groups with the exception of diarrhea, which was more frequent with piperacillin-tazobactam.

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