Treatment of severe nosocomial pneumonia: a prospective randomised comparison of intravenous ciprofloxacin with imipenem/cilastatin

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Abstract

Background—A prospective multicentre study was undertaken to compare the efficacy of intravenous ciprofloxacin or imipenem in the treatment of severe nosocomial pneumonia requiring mechanical ventilation.

Methods—Patients with a clinical suspicion of pneumonia were randomised to receive either ciprofloxacin (800–1200 mg/day) or imipenem (2–4 g/day) in doses adjusted for renal function and specimens of the lower respiratory tract were taken. Patients were included in the study when specimens showed significant growth for potentially pathogenic microorganisms in quantitative bacterial cultures ($n = 75$, ciprofloxacin 41/75 (55%); imipenem 34/75 (45%)). The clinical and bacteriological success rates were the primary and secondary efficacy variables. An intent-to-treat analysis was performed for all randomised patients who received at least one dose of the study medication ($n = 149$, ciprofloxacin 72/149 (48%), imipenem 77/149 (52%)).

Results—The success rates were generally good, but neither the clinical success rates (ciprofloxacin, 29/41 (71%), imipenem, 27/34 (79%); 95% CI -10.8 to 28.1 ; $p = 0.435$) nor the bacteriological response rate (ciprofloxacin, 20/41 (49%), imipenem, 17/34 (50%); 95% CI -21.5 to 23.9 ; $p = 1.0$) were significantly different between the study arms. *Pseudomonas aeruginosa* was recovered in 26/75 patients (35%) and clinical (ciprofloxacin, 10/14 (71%), imipenem, 8/12 (67%); 95% CI -40.4 to 30.9 ; $p = 1.0$) and bacteriological response rates (ciprofloxacin, 7/14 (50%), imipenem, 3/12 (25%), 95% CI -60.9 to 10.9 , $p = 0.247$) were not significantly different in this subgroup of patients. Resistance of *Pseudomonas aeruginosa* developed in 5/26 cases (19%), 1/14 (7%) to ciprofloxacin and 4/12 (33%) to imipenem ($p = 0.147$), and the mortality was 12/75 (16%) with no difference between treatment groups (ciprofloxacin, 8/41 (24%), imipenem 4/34 (17%); $p = 0.362$). The clinical response was evaluable in 109/149 patients (73%) in the intent-to-treat analysis and was successful in 74/109 patients (68%). The clinical response rates were also not significantly different in the intent-to-treat analysis (ciprofloxacin,

34/52 (65%), imipenem, 40/57 (70%); 95% CI -12.8 to 22.3 ; $p = 0.746$).

Conclusions—Treatment with either ciprofloxacin or imipenem was effective in a selected group of patients with microbiologically confirmed, severe nosocomial pneumonia requiring mechanical ventilation. Although no differences between the study medication could be documented in this trial, smaller differences between treatment arms may have been missed because of sample size limitations.

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Keywords: pneumonia; treatment; ciprofloxacin; imipenem

Nosocomial pneumonia is associated with a high mortality despite the availability of broad spectrum antibiotics.¹ The first appropriate treatment measure is the parenteral administration of an empirical antibiotic.² Broad spectrum antibiotic coverage is generally advisable because Gram negative bacteria often cause severe bacterial nosocomial pneumonia and a multibacterial aetiology is frequent. The efficacy of single antibiotic treatment in nosocomial pneumonia is controversial and depends largely on the type of causative microorganisms. Epidemiological approaches have led to the establishment of distinct patient groups with presumed causative agents according to the presence of risk factors, time of onset, and severity of the episode.¹ However, few data are available on the treatment of nosocomial pneumonia with a single drug, regardless of the causative agent.

Ciprofloxacin and imipenem are two broad spectrum antimicrobial agents of different chemical class that have been widely investigated separately for the treatment of lower respiratory tract infections. Some trials have described only initial experiences with either drug^{3–10} while others have used a randomised design for the comparison of either ciprofloxacin or imipenem with another antibiotic.^{11–21} The efficacy of ciprofloxacin and imipenem has been compared directly for the treatment of severe clinical infection,²² pneumonia in ventilated patients,²³ and in one randomised comparison for the treatment of severe pneumonia.²⁴ Treatment with ciprofloxacin was associated with a significantly higher clinical response rate, especially when *Pseudomonas aeruginosa* or Enterobacteriaceae were recovered from the baseline bacterial cul-

ture.²⁴ However, this trial also included patients with community acquired pneumonia, with and without ventilatory support, and, more importantly, did not use quantitative bacterial cultures of lower respiratory tract specimens to confirm pneumonia.

We have therefore compared the efficacy of ciprofloxacin with that of imipenem in a well defined population of patients with microbiologically confirmed, severe nosocomial pneumonia requiring mechanical ventilation.

Methods

PATIENT SELECTION

This study was an open label, prospective, randomised trial for the comparison of efficacy and safety of intravenous ciprofloxacin with that of intravenous imipenem/cilastatin for the treatment of patients with severe nosocomial pneumonia. All adults (aged >18 years) with clinical suspicion of nosocomial pneumonia in nine clinical centres in Spain were eligible for entry into the study. Patients were enrolled during one year and statistical analysis was carried out at one trial centre (AT). The study was approved by the ethical committee and conducted in accordance with its guidelines. The following clinical definitions were applied:

Clinical suspicion of pneumonia: new and persistent infiltrates on the chest radiograph attributable to pulmonary infection and at least two of the following criteria: (1) fever ($\geq 38.3^{\circ}\text{C}$); (2) leukopenia or leukocytosis ($\text{WBC} \leq 4000$ or $\geq 12\,000/\text{mm}^3$, or (3) purulent tracheal secretions.

Nosocomial pneumonia: clinical suspicion of pneumonia present ≥ 72 hours after hospital admission.

Severe nosocomial pneumonia: patients required mechanical ventilation with $\geq 40\%$ Fio_2 to maintain a PaO_2 of ≥ 8 kPa (60 mm Hg).

Microbiologically confirmed nosocomial pneumonia: potentially pathogenic microorganism (PPM) recovered from the lower respiratory tract showed significant growth in quantitative bacterial cultures or if blood cultures or pleural effusions showed bacterial growth (see section on bacteriological procedures for definitions).

All patients with a clinical suspicion of pneumonia were randomised after written informed consent was obtained from the next of kin. Closed envelopes were distributed to each centre before the study to ensure randomisation. Patients were included in the study if the study medication had been given for ≥ 3 days, if pneumonia could be confirmed microbiologically (see definition above), and if the isolated microorganism was sensitive to the study medication (see section on bacteriological procedures for definition).

The following exclusion criteria were applied before randomisation: allergy to a fluoroquinolone, β -lactam or penicillin; patient pregnant or lactating; changes in systemic antibiotic therapy during the five days before enrolment, significant leukopenia ($\leq 1000/\text{mm}^3$), underlying immunocompromising disease or immuno-

suppressive therapy, and application of study medication 30 days before enrolment to the study.

BACTERIOLOGICAL PROCEDURES

Microorganisms were grouped as potentially pathogenic microorganisms (PPMs) and non-PPMs. The following microorganisms were regarded as non-PPMs: *Streptococcus* spp except *Streptococcus pneumoniae*, coagulase negative staphylococci, *Neisseria* spp, and *Candida* spp. Polymicrobial growth was present with two or more PPMs in culture. Lower respiratory tract specimens (tracheobronchial aspirate (TBAS), bronchoalveolar lavage (BAL) fluid, and protected specimen brush (PSB)) were cultured quantitatively for the microbiological confirmation of suspected pneumonia. The growth of PPMs was regarded significant when the following thresholds were exceeded: TBAS $\geq 10^5$ colony forming units (cfu)/ml, PSB $\geq 10^3$ cfu/ml, and BAL fluid $\geq 10^4$ cfu/ml.^{25, 26} Any growth of a PPM in blood or pleural effusion was regarded significant.

Susceptibility testing of bacterial isolates was performed according to standard methods.²⁷ According to the minimal inhibitory concentrations (MIC) the susceptibility was rated sensitive (ciprofloxacin 1 $\mu\text{g}/\text{ml}$ MIC; imipenem 4 $\mu\text{g}/\text{ml}$ MIC), intermediate (ciprofloxacin 2 $\mu\text{g}/\text{ml}$ MIC; imipenem 8 $\mu\text{g}/\text{ml}$ MIC), and resistant (ciprofloxacin 4 $\mu\text{g}/\text{ml}$ MIC; imipenem 16 $\mu\text{g}/\text{ml}$ MIC). Development of resistance was assumed when the bacteria were susceptible or moderately susceptible to the study drug in baseline culture and a strain resistant to the study drug was isolated in one follow up culture.

TREATMENT

The study medication dose was adjusted for all patients according to renal creatinine clearance. The unadjusted doses permitted in this trial were 800–1200 mg per day for ciprofloxacin and 2–4 g/day for imipenem. No other antimicrobial agent was allowed during the study except those initiated more than five days before the study.

EFFICACY PARAMETERS

The clinical response was determined by assessing signs and symptoms of respiratory infection, as well as comparing basal chest radiographs with those obtained at the end of the study. The clinical response was rated as (1) a cure if signs and symptoms related to pulmonary infection had disappeared, (2) failure if lessening of symptoms related to pulmonary infection was rated insufficient or additional treatment was necessary, (3) improved if neither cure nor failure were applicable, and (4) indeterminate if a clinical evaluation was not possible.

The bacteriological response was classified as follows: (1) eradication (elimination of the initial causative microorganism documented in at least one LRTS during the study), (2) presumed eradication (no follow up specimen available and clinical response improved or cure), (3) persistence (continuous isolation of

the basal causative organism), (4) superinfection (elimination of the basal causative agent but isolation of another PPM during follow up), and (5) presumed failure (no follow up specimen available and clinical response failure). Treatment success was assumed if eradication or presumed eradication were present. Treatment failure was rated as persistence, superinfection, or presumed failure.

All adverse clinical events or laboratory abnormalities occurring during treatment or within seven days of discontinuation of the study drug were reported and evaluated for possible association with the study drug.

STATISTICAL METHODS

The primary objective of this study was to compare the clinical response between the two study arms in the predefined study population. An intent-to-treat analysis was performed to disclose possible bias induced by our stringent selection criteria. Indeterminate clinical responses were not included in the calculation of resolution rates. The secondary objective of this study was the comparison of the bacteriological response between the study arms. Moreover, data on safety of the study drugs and mortality within the treatment period were reported.

Data are reported as counts or mean (SD) values. Frequencies were compared using the χ^2 test or Fisher's exact test (expected cell frequency <5) and mean values by the Mann-Whitney U test. Comparisons of success rates

between treatment arms and for recovered organisms are reported with 95% confidence intervals for comparison of proportions. All data were processed using the SPSS version 9.0 on a Windows 95 operating system.

Results

STUDY POPULATION

One hundred and fifty two patients were randomised and three patients never received the study medication (fig 1). The clinical suspicion of pneumonia could not be confirmed microbiologically in 57 of 152 patients (38%) and protocol violation made the exclusion of 13 patients (9%) necessary (one had no need for mechanical ventilation, two had been in hospital <72 hours before ICU admission, three had received concomitant antimicrobial treatment before the study, and in seven cases a pretreatment bacterial culture was not available). The microorganisms found in baseline cultures were resistant to the study medication in three cases (2%) and in 14 (9%) the clinical response was not evaluable (fig 1). The final study population therefore comprised 75/152 patients (49%), 41 of whom (55%) had been randomised to ciprofloxacin and 34 (45%) to imipenem.

To correct for a possible bias induced by the stringent entry criteria an intent-to-treat analysis was performed on all randomised patients who had received at least one dose of the study medication ($n = 149$ (98%), 72 (48%) receiving ciprofloxacin and 77 (52%) receiving imipenem).

The clinical characteristics between the two study arms for both populations are shown in table 1. No significant differences were found in either the study population or in the population included in the intent-to-treat analysis. Severity of respiratory failure as measured by the alveolar-arterial oxygen tension gradient ($P(A-a)O_2$) and the fractional inspired oxygen ratio (FiO_2) and severity of the illness as measured by the APACHE II score were not significantly different.

ANALYSIS OF STUDY POPULATION

Study medication

The mean duration of treatment was not significantly different between the ciprofloxacin and imipenem groups (9.3 (3.8) versus 10.1 (3.2) days; $p = 0.372$). The mean daily dose was 1035 (163) mg/day (14.5 (3.4) mg/kg/day) for ciprofloxacin and 2655 (674) mg/day (38.4 (10.6) mg/kg/day) for imipenem.

Bacteriological data

The microorganisms recovered in the baseline culture are shown in table 2. The most commonly recovered causative organisms in the study population were *P aeruginosa* ($n = 26$), *Haemophilus influenzae* ($n = 21$), and *S pneumoniae* ($n = 15$). All microorganisms were sensitive to the study medication (see definition of study population). Although there was a trend towards a higher frequency of *H influenzae* isolates in the imipenem group, no statistically significant differences were detected. The proportion of cultures with polymicrobial

Figure 1 Trial profile. Only patients with microbiologically confirmed pneumonia were included in the study population ($n = 75$). The intent-to-treat analysis was performed on all patients who had been randomised and received at least one dose of the study medication ($n = 149$). The total number of patients excluded in smaller than the sum of individual causes because there were multiple causes in some patients.

Table 1 Demographic characteristics of the study population and the intent-to-treat population

	Study population (n=75)		Intent-to-treat population (n=149)	
	Ciprofloxacin (n=41)	Imipenem (n=34)	Ciprofloxacin (n=72)	Imipenem (n=77)
Men, n (%)	31 (75.6%)	25 (73.5%)	53 (73.6%)	57 (74.0%)
Women, n (%)	10 (24.4%)	9 (26.5%)	19 (26.4%)	20 (26.0%)
Mean (SD) age (years)	64 (14)	61 (17)	60 (16)	62 (16)
Mean (SD) weight (kg)	74 (13)	71 (10)	72 (12)	71 (11)
Mean (SD) BMI (kg/m ²)	26.7 (4.6)	25.9 (3.5)	26.1 (4.0)	26.0 (3.8)
No with one or more comorbid illness	41 (100%)	30 (88%)	70 (97%)	71 (92%)
Type of comorbid illness*, n (%)				
COPD	16 (39%)	12 (35%)	20 (28%)	29 (38%)
Other respiratory illness	3 (7%)	1 (4%)	2 (3%)	2 (3%)
Cardiovascular/vascular	14 (34%)	16 (47%)	28 (39%)	33 (43%)
Neurological	10 (24%)	10 (29%)	17 (24%)	23 (30%)
Diabetes mellitus	6 (15%)	6 (18%)	9 (13%)	7 (9%)
Gastrointestinal	9 (2%)	3 (9%)	10 (14%)	4 (5%)
Neoplasm	7 (17%)	0	12 (17%)	4 (5%)
Renal	2 (5%)	0	2 (3%)	4 (5%)
Other	3 (7%)	0	3 (4%)	1 (1%)
Mean (SD) P(A-a)O ₂	218 (113)	215 (154)	257 (157)	213 (144)
Mean (SD) Pao ₂ /Fio ₂ ratio	206 (93)	223 (86)	204 (101)	229 (124)
Mean (SD) APACHE score	13.8 (7.5)	13.9 (8.6)	13.9 (7.7)	14.7 (7.6)
Mean (SD) leucocyte count/mm ³ †	14.5 (5.9)	12.6 (5.5)	14.5 (5.6)	12.6 (4.9)
Mean (SD) creatinine (mg/dl)	1.3 (1.2)	0.9 (0.4)	1.2 (1.1)	1.0 (0.6)
Mean (SD) body temperature (°C)	37.8 (0.9)	37.9 (1.1)	37.8 (1.0)	37.8 (0.9)
Mean (SD) PEEP (cm H ₂ O)	5.7 (2.8)	5.7 (3.3)	6.2 (3.1)	6.0 (3.4)
(no (%) patients with PEEP)	(15 (36.6%))	(17 (45.9%))	(34 (47.2%))	(29 (37.6%))
No (%) patients with PEEP ≥ 5 cm H ₂ O	22 (53.7%)	18 (52.9)	38 (52.8%)	36 (46.8)

BMI = body mass index; P(A-a)O₂ = alveolar-arterial oxygen tension gradient; Pao₂ = arterial oxygen tension; Fio₂ = fractional inspired oxygen concentration; PEEP = positive end expiratory pressure required on enrollment to the study.

*Sum of single percentages higher than 100% due to multiple comorbid illnesses.

†Mann-Whitney U test, p = 0.165.

Table 2 Microorganisms recovered in the study population

	Ciprofloxacin (n=41)	Imipenem (n=34)	p value
PPMs			
<i>Pseudomonas</i> spp	14	12	0.917
<i>Acinetobacter</i> spp	6	3	0.498*
<i>Stenotrophomonas maltophilia</i>	1		1.0*
Methicillin resistant <i>Staphylococcus aureus</i> (MRSA)	1		1.0*
Other Gram negative organisms			
<i>Haemophilus influenzae</i>	8	13	0.074
<i>Klebsiella pneumoniae</i>	1	1	1.0*
<i>Enterobacter</i> spp	3		0.246*
<i>Escherichia coli</i>	1	1	1.0*
<i>Serratia marcescens</i>	1		1.0*
<i>Proteus mirabilis</i>		1	1.0*
<i>Citrobacter freundii</i>	1		1.0*
Gram positive organisms			
<i>Streptococcus pneumoniae</i>	7	8	0.486
Methicillin sensitive <i>Staphylococcus aureus</i> (MSSA)	1		1.0*
Fungi			
<i>Aspergillus fumigatus</i>	1		1.0*
Non-PPMs			
Coagulase negative <i>Staphylococcus</i> spp	5	7	0.326
<i>Streptococcus</i> spp		1	1.0*
<i>Enterococcus faecalis</i>	2	4	0.401*
<i>Corynebacterium</i> spp		1	1.0*
<i>Achromobacter</i> spp		1	1.0*
<i>Neisseria</i> spp		1	1.0*
Other non-PPMs	1		1.0*
Fungi			
<i>Candida albicans</i>	1		1.0*

All had at least one potentially pathogenic microorganism (PPM) with growth above the defined thresholds in quantitative bacterial cultures (see definition of study population).

Total number of microorganisms recovered does not equal the number of patients in every group due to polybacterial growth.

p values were calculated with χ^2 test or Fisher's exact test* where appropriate.

growth was similar in both study arms (ciprofloxacin: 10/41 (24%), imipenem: 8/34 (24%); p = NS).

Analysis of clinical response

Fifty six of the 75 patients (75%) showed a successful clinical response and the clinical response rate with ciprofloxacin (71%) was not statistically different from that with imipenem (79%, 95% CI -10.8 to 28.1, table 3). *P aeruginosa* was the causative agent in 26 of the 75 cases (35%) and the clinical response with

ciprofloxacin (10/14, 71%) was not significantly different from that with imipenem (8/12, 67%, p = 1.0) in this subgroup of patients (table 3). Enterobacteriaceae were causative agents in seven cases (9%) and the success rate did not differ significantly between treatment arms (table 3).

Analysis of bacteriological response

The bacteriological response was rated a success in 37 patients (49%) and was not significantly different between the two treatment groups (table 3, ciprofloxacin 20/41 (49%), imipenem 17/34 (50%)). Analysis of the treatment failures showed persistence of the microorganism more often in the imipenem group (8/34 (24%)) than in the ciprofloxacin group (2/41 (5%), 95% CI 2.9 to 34.4, p = 0.035). The frequencies of superinfection (95% CI -24.6 to 10.1, p = 0.422) and presumed failure (95% CI -29.7 to 4.4, p = 0.162) were not significantly different between the two study groups (table 3). Analysis of treatment failure due to persistence revealed that eight of 10 patients (80%) had *P aeruginosa* and two (20%) had *Acinetobacter* spp in initial bacterial culture. Causative microorganisms for both arms in patients with presumed treatment failure were: *P aeruginosa* 6/14 (43%), *H influenzae* 3/14 (21%), *S pneumoniae*, *Stenotrophomonas maltophilia*, *Enterobacter* sp, *Acinetobacter baumannii*, methicillin resistant *Staphylococcus aureus*, and methicillin sensitive *S aureus* all 1/14 (7%).

The bacteriological response rate in the ciprofloxacin arm (7/14, 50%) was not significantly higher than in the imipenem arm (3/12, 25%, 95% CI -60.9 to 10.9, p = 0.247) in the subgroup of patients with *P aeruginosa* pneumonia. This was also the case in the subanalysis of cases with Enterobacteriaceae in the baseline culture. Although the bacteriological

Table 3 Success rates for the clinical and bacteriological responses in the two study arms

	Ciprofloxacin	Imipenem	p value* (95% CI)
Clinical response:			
Success rate	29/41 (71%)	27/34 (79%)	0.435 (-10.8 to 28.1)
Cure	17/41 (42%)	22/34 (65%)	
Improvement	12/41 (29%)	5/34 (14%)	
<i>Pseudomonas aeruginosa</i> (n=26)			
Success rate	10/14 (71%)	8/12 (67%)	1.0 (-40.4 to 30.9)
Enterobacteriaceae (n=9)			
Success rate	5/6 (83%)	2/3 (67%)	1.0 (-77.8 to 44.4)
Bacteriological response:			
Success	20/41 (49%)	17/34 (50%)	1.0 (-21.5 to 23.9)
Eradication	7/41 (17%)	10/34 (29%)	
Presumed eradication	13/41 (32%)	7/34 (21%)	
Failure	21/41 (51%)	17/34 (50%)	
Persistence	2/41 (5%)	8/34 (24%)	
Superinfection	9/41 (22%)	5/34 (15%)	
Presumed failure	10/41 (24%)	4/34 (11%)	
<i>Pseudomonas aeruginosa</i> (n=26)			
Success rate	7/14 (50%)	3/12 (25%)	0.247 (-60.9 to 10.9)
Enterobacteriaceae (n=9)			
Success rate	5/6 (83%)	1/3 (33%)	0.266 (-111.1 to 11.1)

In addition, subanalysis of patients with *Pseudomonas aeruginosa* and Enterobacteriaceae in baseline culture are shown.

*p values calculated using χ^2 test.

success rate was 83% in the ciprofloxacin group (5/6 cases) compared with 33% (1/3 cases) in the imipenem group, the number of observations was too small to yield a significant difference ($p = 0.266$, 95% CI -111.1 to 11.1).

Development of resistance

Development of resistance was observed in five of 26 patients (19%) with initial isolates of *P. aeruginosa* with no significant differences between treatment groups (ciprofloxacin 1/14 (7%) versus imipenem 4/12 (33%); $p = 0.147$). *Acinetobacter* spp were causative microorganisms in nine patients but only three (33%) had evaluable follow up cultures. In these three patients no resistance developed during the study period. No resistant strains of Enterobacteriaceae were isolated in eight evaluable follow up cultures.

Adverse effects and mortality

A total of 10 adverse events were reported in 75 patients (13%) during the study period which were rated to have a possible relationship with the study drug. These figures did not differ significantly between the treatment groups (ciprofloxacin 6/41 (15%), imipenem 4/34 (12%); $p = 0.494$). The adverse events reported in the ciprofloxacin group were septic shock ($n = 3$), gastrointestinal bleeding ($n = 1$), renal failure ($n = 1$), and angina ($n = 1$). In the imipenem group cardiac arrest ($n = 1$), a significant increase in laboratory variables ($n = 1$), and multiorgan failure ($n = 1$) were reported. No seizures were observed during the study in either treatment group. The overall crude mortality was 12/75 (16%) with no significant differences between treatment arms (ciprofloxacin 8/41 (20%), imipenem 4/34 (12%); $p = 0.362$). The most frequent causes of death were shock (8/29, 18%), multiple organ failure (5/29, 17%), cardiac arrest (4/29, 14%), and respiratory failure (2/29, 7%) with no significant differences between the treatment groups.

ANALYSIS OF THE INTENT-TO-TREAT POPULATION
The mean duration of treatment was not significantly different between the treatment groups in the intent-to-treat population (ciprofloxacin 8.4 (4.2) days versus imipenem 9.3 (4.2) days; $p = 0.297$). The clinical response was evaluable in 109 of the 149 patients (73%) (ciprofloxacin 52/72 (72%), imipenem 57/77 (74%); $p = 0.803$) and seven of the 149 patients (5%) had no evaluable basal bacterial culture (ciprofloxacin 3/72 (4%), imipenem 4/77 (5%); $p = 0.755$). At least one PPM was recovered in 48 of 69 patients in the ciprofloxacin group (70%) and in 43 of 73 patients in the imipenem group (59%; $p = 0.780$). The predominantly recovered causative organisms in the study population were *P. aeruginosa* ($n = 32$), *H. influenzae* ($n = 24$), and *S. pneumoniae* ($n = 15$).

The overall clinical success rate in the intent-to-treat population (74/109 evaluable patients, 68%) was not significantly different from the success rate in the study population (75%, 95% CI -6.1 to 20.1, $p = 0.321$). The clinical success rate of treatment with imipenem (40/57, 70%) was not significantly higher than the success rate with ciprofloxacin (34/52, 65%, 95% CI -12.8 to 22.3; $p = 0.746$).

A total of 35 adverse events were reported with no significant difference between the study arms (ciprofloxacin 21/72 (29%), imipenem 14/77 (18%); $p = 0.113$). Changes in laboratory values of possible clinical significance were 5/21 (24%) reported adverse effects in the ciprofloxacin group and 6/14 (42%) in the imipenem group ($p = 0.283$). Shock and multiorgan failure were reported in 5/14 (36%) events in the ciprofloxacin group and 3/14 (42%) events in the imipenem group ($p = 0.577$).

Discussion

The success rate of the clinical response to treatment of severe nosocomial pneumonia in patients requiring mechanical ventilation was not significantly different between ciprofloxacin (29/41, 71%) and imipenem (27/34, 79%). This was true for the study population and the intent-to-treat population. No differences were found in the bacterial response rate to ciprofloxacin (20/49, 49%) or imipenem (17/34, 50%) in this study population.

Despite the introduction of potent broad spectrum antimicrobial agents and the use of preventive measures, nosocomial pneumonia remains an important cause of mortality and morbidity in the ICU.^{1 28 29} The causative microorganism varies according to the individual patient risk profile. The severity, type, and number of risk factors and the time of onset of nosocomial pneumonia may influence the risk profiles. Gram negative bacilli, Enterobacteriaceae, *H. influenzae*, and methicillin sensitive *S. aureus* are frequent causative agents in nosocomial pneumonia. *P. aeruginosa* and other potentially drug resistant microorganisms play an important part in patients receiving prolonged mechanical ventilation and antibiotic pretreatment.³⁰ Nosocomial pneumonia is sen-

sitive to empirical treatment with parenteral broad spectrum antibiotic drugs, but the use of a single drug is controversial.¹ Single drug treatment may be less efficient in patients with *P aeruginosa* or polymicrobial growth, but it may also be beneficial by reducing toxicity and expense.³¹

The clinical success rate for both drugs was good in our study population, with no differences between the two. Our study included a very homogeneous study population consisting only of patients with microbiologically confirmed nosocomial pneumonia on mechanical ventilation. This is an important difference from previous studies as we used lower respiratory tract specimens together with quantitative bacterial cultures to confirm pneumonia. We could not confirm the superiority of ciprofloxacin over imipenem as described by Fink *et al* in a large population of patients with a clinical diagnosis of community or nosocomial pneumonia on and off mechanical ventilation.²⁴ On the contrary, in our patients with severe nosocomial pneumonia there was a trend in favour of imipenem but our study was too small to detect small differences. However, the percentage of positive clinical responses in our study was comparable to theirs²⁴ and to other studies investigating treatment with a single antibiotic of the same class in at least in one arm. Cometta *et al*²³ compared the efficacy of imipenem with a combination of imipenem plus netilmicin in patients with severe nosocomial pneumonia or sepsis and reported a clinical success rate of 80% with imipenem alone and 86% with the combination. Colardyn and Faulkner compared two carbapenem regimens in the treatment of nosocomial bacterial infection.¹¹ The clinical response rates were comparable for imipenem/cilastatin (75%) and meropenem (75%) in the subanalysis of nosocomial pneumonia.

As in other studies, the bacteriological eradication rates were substantially lower than the clinical success rates but were also comparable for both treatments. Although the clinical success rates were generally not affected by the recovery of Gram negative bacilli, certain restrictions with respect to the bacteriological response apply. When *P aeruginosa* was identified as the causative agent in the baseline culture there was a non-significant trend towards a lower eradication rate with imipenem (25% versus 50%; $p = 0.247$). This observation is in accordance with the results of Fink *et al* who found a better eradication rate with ciprofloxacin than with imipenem in the presence of *P aeruginosa* in a multivariate model.²⁴ However, we used extremely stringent entry criteria and the number of cases was too small in the subanalysis of patients with *P aeruginosa* to confirm conclusively the results of Fink *et al*.²⁴

The development of resistance is a major concern when single antibiotics are prescribed. *P aeruginosa* resistance developed in five of 26 patients (19%) with no significant differences between the treatment arms. However, even combination therapy with an antipseudomonal agent may not result in bacteriological cure. Cometta and coworkers found the emergence

of *P aeruginosa* resistant to the study drug to be less frequent with imipenem alone (9%) than with imipenem plus netilmicin (15%).¹² No case of resistance of Enterobacteriaceae was identified in our study. However, the number of evaluable cultures with Enterobacteriaceae was small and the data must be interpreted with caution.

Both ciprofloxacin and imipenem in the doses administered could be regarded as safe and the incidence of severe adverse events was not significantly different between the two drugs. The absence of seizures even with high doses in this study may be due to sedation during mechanical ventilation. The overall mortality was 16% which did not differ between the two arms of the study.

Some possible limitations of this study should be considered. Firstly, our study was considerably smaller than the investigation published by Fink *et al*²⁴ and does not therefore have the power to detect small differences. However, our study analysed only patients with microbiologically confirmed pneumonia, which has become the diagnostic standard. Secondly, the lower respiratory tract of all patients was sampled before starting the study medication. We were therefore able to adjust the antibiotic in cases with resistant microorganisms. The number of patients with resistant microorganisms was small, but we have to assume that these cases would have been undetected without microbiological examination. Treatment with a single antibiotic may therefore not be the ideal empirical choice for patients with severe nosocomial pneumonia in institutions without routine microbiological sampling. Thirdly, we could not establish differences between the treatment groups in a subanalysis of patients with *P aeruginosa* in the baseline culture. However, this was not the primary objective of the study and larger trials are needed to study this further.

In conclusion, treatment with either ciprofloxacin or imipenem yielded good clinical success rates in selected patients with microbiologically confirmed nosocomial pneumonia on mechanical ventilation. We were not able to reach conclusive results from the subanalysis of patients with nosocomial pneumonia caused by *P aeruginosa*. Physicians should be prepared to broaden antibiotic regimens in these cases because insufficient data are available to rule out the possibility that treatment with a single antibiotic facilitates the development of resistance in patients with nosocomial pneumonia caused by *P aeruginosa*.

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