Population Pharmacokinetics and Pharmacodynamics of Continuous versus Short-Term Infusion of Imipenem-Cilastatin in Critically Ill Patients in a Randomized, Controlled Trial[†]

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Beta-lactams are regularly administered in intermittent short-term infusions. The percentage of the dosing interval during which free drug concentrations exceed the MIC ($fT_{>MIC}$) is the measure of drug exposure that best correlates with clinical outcome for beta-lactams. Therefore, administration by continuous infusion has gained increasing interest recently. We studied 20 critically ill patients with nosocomial pneumonia and investigated whether continuous infusion with a reduced total dose, compared to the standard regimen of intermittent short-term infusion, results in a superior probability of target attainment as assessed by the $fT_{>MIC}$ value of imipenem. In this prospective, randomized, controlled clinical study, patients received either a loading dose of 1 g/1 g imipenem and cilastatin (as a short-term infusion) at time zero, followed by 2 g/2 g imipenem-cilastatin per 24 h as a continuous infusion for 3 days ($n = 10$), or 1 g/1 g imipenem-cilastatin three times per day as a short-term infusion for 3 days (total daily dose, 3 g/3 g; $n = 10$). Imipenem concentrations in plasma were determined by using a validated liquid chromatography-tandem mass spectrometry assay. A two-compartment open model was employed for population pharmacokinetic modeling. We simulated 10,000 intensive-care-unit patients via Monte Carlo simulations for pharmacodynamic evaluation using the target 40% $fT_{>MIC}$. The probability of target attainment by MIC for intermittent infusion was robust (>90%) up to MICs of 1 to 2 mg/liter. The corresponding value for continuous infusion was 2 to 4 mg/liter. Although all 20 patients had an $fT_{>MIC}$ of 100%, 3 patients died. Patient survival was best described by employing a sepsis-related organ failure assessment score as a covariate in a logistic regression analysis. Larger clinical trials are warranted for evaluation of continuous infusions at a reduced dose of imipenem for critically ill patients.

In critically ill patients, intensive care unit (ICU)-acquired pneumonia has been shown to be associated with a significant increase in the length of stay and mortality (27). Besides other factors, early and adequate antibiotic treatment has a major prognostic impact and is therefore of particular clinical relevance (12, 14). Furthermore, adequacy of antibiotic treatment is also determined by sufficient distribution to the site of action. Since antibiotic concentrations at the site of action are often difficult to determine, concentrations in plasma are most commonly used as a surrogate measure.

Broad-spectrum β -lactam antibiotics are considered appropriate in the treatment of ICU-acquired pneumonia. However, the optimal method for administration of β -lactam antibiotics is currently under investigation. Although they are usually administered in clinical practice in regular intermittent short-

term infusions following the manufacturers' instructions, the administration of β -lactam antibiotics by continuous infusion has been proposed (4, 15, 21). Previous studies (3, 7, 17, 28) repeatedly emphasized that the time that the antibiotic concentration exceeds the MIC best predicts the microbiological and clinical success of β -lactams.

Besides the probable improvement in survival rates achieved by optimizing plasma levels, economic aspects must also be considered. A reduced amount of β -lactam antibiotics may be administered via continuous-infusion treatment with the same probability of target attainment. However, the economic implications of a shorter stay in the ICU are much lower costs. In principle, the effectiveness of imipenem for critically ill patients with pneumonia has been clearly documented (19, 20, 22).

To achieve an "optimal" probability of successful therapy with β -lactams, it is considered necessary to maintain plasma imipenem concentrations above a threshold concentration throughout the dosing interval. Data from a lung infection model with neutropenic mice (3) show that stasis against *Enterobacteriaceae* is achieved when the free drug concentration exceeds the MIC for approximately 30% of the dosing interval for penicillins, 35 to 40% for cephalosporins, and 20% for carbapenems. A drop in the bacterial counts by about 2 log₁₀ at 24 h is achieved with this mouse infection model if these percentages are circa 50% for penicillins, 60 to 70% for cep-

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alosporins, and 40% for carbapenems. Since the percentage of the dosing interval during which free drug concentrations exceed the MIC ($fT_{>MIC}$) is most closely linked to organism killing, we wished to compare the pharmacokinetic and pharmacodynamic characteristics of imipenem in ICU patients via Monte Carlo simulations when imipenem was given either intermittently at 1 g every 8 h (q8h) (daily dose, 3 g) via short-term infusions or as continuous infusion at a lower daily dose of 2 g (after a 1-g loading dose). Additionally, we explored which patient covariates best predicted patient survival and imipenem clearance.

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MATERIALS AND METHODS

Patients. The study was performed in a surgical intensive care unit at the University Hospital of Jena, Germany. The local institutional ethics committee approved this study. The study was conducted following the guidelines of the Declaration of Helsinki. Written informed consent was obtained from each patient's next-of-kin. Inclusion criteria were ICU-acquired pneumonia (duration of endotracheal intubation and mechanical ventilation of >3 days) and normal renal function. In our study, pneumonia was defined as the presence of infiltrates in the chest X-ray and positive microbiology tests for bacteria in tracheal or bronchial secretions. No patients with renal replacement therapy were enrolled. For each patient, creatinine clearance was calculated by measuring 12-h urine volume, and urine and plasma creatinine concentrations were each determined immediately prior to the beginning of the study. Body surface area was calculated by using the DuBois and DuBois formula (10). For each patient, the simplified acute physiology score, acute physiology and chronic health evaluation score, and sepsis-related organ failure assessment (SOFA) score were determined.

Drug administration and dosage. All patients received imipenem-cilastatin (Zienam; MSD, Munich, Germany) for treatment of ICU-acquired pneumonia. We randomized 20 adults into a continuous-infusion group and a short-term-infusion group.

The patients in the continuous-treatment group ($n = 10$) received a loading dose of 1 g/1 g imipenem and cilastatin (as a short-term infusion; infusion time, 40 min) at time zero, followed by 2 g/2 g imipenem-cilastatin per 24 h as a continuous infusion for 3 days. The continuous infusion of imipenem-cilastatin at an infusion rate of 83.3/83.3 mg/h started at 4 h post-start of the loading dose. The total dose in the continuous-treatment group was 1 g/1 g loading dose plus 6 g/6 g maintenance dose as a continuous infusion over 72 h, i.e., 7 g/7 g imipenem-cilastatin within 76 h. Thereafter, the patients in the continuous-infusion group received intermittent doses of 1 g/1 g imipenem-cilastatin q8h.

The patients in the intermittent-treatment group ($n = 10$) received 1 g/1 g imipenem-cilastatin as a short-term infusion (infusion time, 40 min) three times daily for 3 days. These patients received nine short-term infusions between time zero and 72 h. The total dose in the intermittent-treatment group was 9 g/9 g imipenem-cilastatin within 72 h. This dosage regimen is a standard dose and schedule administered in clinical practice.

In both groups, imipenem was given through a separate lumen of a central venous catheter (Certofix Trio; Braun Melsungen, Germany). All doses were administered via an automatic high-precision infusion pump (Perfusor fm; Braun, Melsungen, Germany).

For the intermittent-dosage regimen, two dose units, each containing 0.5 g/0.5 g imipenem-cilastatin, were dissolved in 100 ml (each) of sterile 0.9% NaCl solution immediately before each short-term infusion. The two dose units were each infused over 20 min, yielding a dose of 1 g/1 g imipenem-cilastatin given over 40 min for each short-term infusion.

For the continuous-infusion regimen, 0.25 g/0.25 g imipenem-cilastatin was dissolved in 50 ml of sterile saline q3h due to the instability of imipenem. The reconstituted imipenem solution was kept at 21°C during the infusion (the temperature of the ICU ward). According to the German prescribing information (German product information; Zienam; MSD), the infusion solution is sufficiently stable for 4 h at 25°C.

Blood sampling. All patients had an arterial line for clinical indication, which allowed blood sampling for determination of plasma imipenem concentrations. Five milliliters of arterial blood were collected predose (0 h) and at 4, 10, 16, 22,

46, and 70 h after the start of the first dose. The arterial blood samples were collected in Li-heparinate tubes (Sarstedt, Nümbrecht, Germany) and immediately cooled in an ice-water bath for at least 5 min. The samples were centrifuged for 10 min at 3,800 rpm and +4°C. A volume of 500 μ l of the resulting plasma was added to 500 μ l of stabilizer solution (morpholinopropanesulfonic acid buffer, 1.0 M, pH 7.0). The resulting mixture of 1 ml was intensively agitated for at least 15 s by an automatic shaker and then immediately frozen on dry ice and stored at -70°C .

Determination of imipenem in plasma by LC-MS/MS. Imipenem concentrations in plasma were determined by high-performance liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS). All sample handling and thawing of frozen plasma samples were done at +4°C. Plasma samples were stabilized by addition of 1 M morpholinopropanesulfonic acid buffer (pH 7.0) at the clinical study site. A volume of 0.1 ml of the stabilized plasma was deproteinized by addition of 0.2 ml of acetonitrile containing the internal standard. After thorough mixing, the samples were centrifuged for 5 min at 3,600 rpm at approximately +4°C. Fifteen microliters of each sample was chromatographed on a reversed-phase column (Grom-SIL 80 Amino-3 CP, 5 μ m, 40 by 4.6 mm; Alltech Grom GmbH, Rottenburg-Hailfingen, Germany), eluted with an isocratic solvent system consisting of 0.01 M ammonium acetate buffer and acetonitrile (1:1 [vol:vol]), and monitored by LC-MS/MS with a selected reaction monitoring method as follows: precursor $\rightarrow$ product ion for imipenem, m/z 300 $\rightarrow$ m/z 98, and for the internal standard, m/z 351 $\rightarrow$ m/z 265; both analyses were in positive mode.

Under these conditions, imipenem and the internal standard were eluted after approximately 2.3 min and 1.6 min, respectively. The Mac Quan software (version 1.4-noFPU, 1991 to 1995; Perkin-Elmer, Toronto, Canada) was used for evaluation of chromatograms. Calibration was performed by weighted (1/concentration²) linear regression. The limit of quantification for plasma samples was 0.100 mg/liter. The response from calibration standards was linear from 0.100 to 100.0 mg/liter, and the coefficient of correlation for all measured sequences was at least 0.997. The interday precision and the analytical recovery of the spiked quality control standards of imipenem in plasma ranged from 4.9 to 9.8% and were 101.3% (100.0 μ g/ml), 93.5% (40.0 μ g/ml), 96.1% (5.00 μ g/ml), and 100.8% (0.200 μ g/ml), respectively.

Pharmacokinetic calculations. The NPAG (nonparametric adaptive grid with adaptive γ) program of Leary et al. was employed for the analysis (14a). Because of prior data relating to imipenem pharmacokinetic modeling (2, 5, 6, 8, 9, 13, 18, 24), a two-compartment open model with a time-delimited zero-order input (intermittent administration) or a short (40-min; see above) intravenous infusion followed by a continuous drug infusion starting at 4 h was employed. In both instances, first-order elimination was employed in the model.

The initial choice of weights was determined as being proportional to the inverse of the assay variance. Briefly, the nominal concentrations and their between-day standard deviations were modeled as one-, two-, three-, or four-parameter polynomials. The polynomial chosen was identified by the Akaike information criterion (29). This polynomial was multiplied by a scalar value, γ , which was iteratively determined with each cycle. In this way, a good approximation to the homoscedastic assumption was obtained. Bayesian estimates were obtained employing the "population of one" utility within NPAG. The model fit was examined by regression analysis after the Bayesian step and by visual examination of each subject's estimates. The weighted mean error was used as a measure of bias, and the bias-adjusted weighted mean squared error was employed as a measure of precision.

Since clearance directly determines the steady-state drug concentration after continuous infusion, we tried to identify patient covariates which can be used to predict imipenem clearance. We used a general linear model and studied sex, age, weight, height, body surface area, and creatinine clearance measured as 12-h collections as covariates for their ability to predict imipenem clearance.

Pharmacodynamic analysis. The final mean parameter vector and full covariance matrix were inserted into Subroutine PRIOR of the ADAPT II package of programs of D'Argenio and Schumitzky (D. Z. D'Argenio and A. Schumitzky, ADAPT II, a program for simulation, identification, and optimal experimental design, Biomedical Simulations Resource, University of Southern California, Los Angeles, 1992). Monte Carlo simulations (10,000 simulated subjects) were performed for both modes of administration. Normal and log-normal distributions for the between-patient variability were evaluated. The choice of distribution was determined by the fidelity with which the original mean parameter vector and the variances of the parameter values were recapitulated by the simulations with the different distributions.

We studied the pharmacodynamic $fT_{>MIC}$ targets of 20%, 30%, and 40% for imipenem concentrations. Based on data from a model of lung infection in neutropenic mice from Craig and colleagues (3, 4a), an $fT_{>MIC}$ of 40% of the

TABLE 1. Patients' demographic data^a

Parameter	Value for group (<i>n</i> ^b)	
	Intermittent treatment (10)	Continuous infusion (10)
Sex (f/m)	5/5	4/6
Age (yr)	59 ± 16 (38–78)	62 ± 16 (34–80)
Height (cm)	170 ± 7 (158–184)	171 ± 8 (160–180)
Weight (kg)	78 ± 14 (60–105)	73 ± 8 (60–90)
BSA (m ²)	1.89 ± 0.16 (1.60–2.13)	1.84 ± 0.14 (1.60–2.09)
SAPS II score	43 ± 12 (22–62)	44 ± 14 (28–77)
APACHE II score	28 ± 5 (20–33)	26 ± 6 (18–36)
SOFA score	6 ± 3 (1–10)	7 ± 2 (4–10)
Creatinine clearance (ml/min)	128 ± 35 (91–187)	122 ± 33 (75–177)
ICU-LOS (days)	12 ± 7 (4–24)	14 ± 8 (7–35)
Outcome (no. of survivors/no. of nonsurvivors)	8/2	9/1

^a Data are given as average ± standard deviation (range). f/m, no. female/no. male; BSA, body surface area (calculated by the DuBois and DuBois formula); APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology Score; ICU-LOS, ICU length of stay at beginning of study.

^b *n*, no. of patients in group.

dosing interval represents the target for a drop in bacterial counts by about 2 log₁₀ at 24 h for carbapenems, and an $fT_{>MIC}$ of 20% represents the target for bacteriostasis. In addition to studying the $fT_{>MIC}$, we derived the percentage of the dosing interval during which free drug concentrations exceeded four times the MIC ($fT_{>4 \times MIC}$) from the individual predicted concentration-time profiles for our 20 patients. The protein binding of imipenem was reported to be about 20% or less (imipenem and cilastatin [Zienam] product information, June 2006; MSD) (23). As a conservative approach, we assumed a fixed protein binding of 20% in our Monte Carlo simulations. The MICs were determined by using the Bouillon dilution test (Micronaut-S, GENARS GP4 and GP5; Fa. Merlin, Bornheim-Hersel, Germany).

Statistical analysis. All statistical analyses were performed with SYSTAT 10.2 for Windows, SigmaStat for Windows (version 1.0), or WinNonlin Pro (version 5.0.1). We calculated the between-subject variability and between-occasion variability of the observed concentrations for the continuous-infusion group by analysis-of-variance statistics on a log scale. Concentrations at 4 h after the first dose were omitted due to the influence of the loading dose. Each study day was treated as one occasion.

We studied the influence of covariates on imipenem clearance using a general linear model approach with demographic data as covariates. Linkage of covariates to survivorship was performed using logistic regression analysis. Breakpoints were sought for continuous variables using a recursive partitioning algorithm (classification and regression tree [CART] analysis). All analyses were performed univariately. Patients' characteristics were compared by using the Mann-Whitney U test. A *P* value of 0.05 or less was considered statistically significant.

RESULTS

Patient demographics. The patients were randomly assigned to one of the two treatment groups. The randomization code was provided to the clinical investigator in sealed envelopes. Both groups were evenly matched with regard to demographic data and severity of critical illness (Table 1). In particular, renal function was comparable in both groups. ICU admission diagnosis was subarachnoid hemorrhage (*n* = 2), traumatic brain injury (*n* = 5), intracranial hemorrhage (*n* = 2), or lung cancer surgery (*n* = 1) in the continuous-infusion group. In the short-term infusion group, ICU admission was due to subarachnoid hemorrhage (*n* = 2), traumatic brain injury (*n* = 3), lung cancer surgery (*n* = 1), stroke (*n* = 1), cervical spine surgery (*n* = 1), aortic aneurysm repair (*n* = 1), or abdominal surgery due to ulcer duodeni (*n* = 1).

Antibiotic pretreatment was given to eight patients in the short-term-infusion group (four patients pretreated with ceftri-

FIG. 1. Observed concentrations in plasma (average ± SD) and typical predicted concentration-time profiles for imipenem after continuous and intermittent treatment of critically ill patients with normal renal function (see Materials and Methods for details on dosage regimens). The typical concentration-time profile based on the median pharmacokinetic parameters was predicted for the continuous-infusion group (continuous line) and for the intermittent-treatment group (dashed line). Importantly, this line is not equivalent to the average predicted concentrations for a large number of simulated patients. The two lines fall on top of each other during the first 4 h.

axone, one with cefuroxime, two with piperacillin-tazobactam, and one with moxifloxacin). For comparison, nine patients in the continuous group received antibiotic therapy before administration of imipenem-cilastatin (four patients pretreated with ceftriaxone, two with cefuroxime, two with piperacillin-tazobactam, and one with cefepime).

Drug concentrations. Plasma imipenem concentration curves over the 72-h interval are shown in Fig. 1 for both groups (continuous and intermittent treatment). In the continuous-infusion group, the average plasma imipenem concentration for all samples between 10 and 70 h after the start of the first dose was 8.65 ± 3.54 mg/liter. No patient in the continuous-infusion group had a plasma imipenem concentration below 2 mg/liter.

The total variability (including variability from the assay) of the individual concentrations had a coefficient of variation of 41%, between-patient variability was 35%, and between-occasion variability was 20%. Therefore, between-patient variability accounted for about 75% of the total variance, and between-occasion variability accounted for about 25% of total variance of the observed concentrations for the continuous-infusion group.

Pharmacokinetic parameter values. The overall mean and median parameter values, their standard deviations, and the full variance-covariance matrix are presented in Tables 2 and

TABLE 2. Pharmacokinetic parameter values and their dispersions^a

Mean or dispersion	Vc (liters)	Kcp (h ⁻¹)	Kpc (h ⁻¹)	CL (liters h ⁻¹)
Mean	12.2	7.69	8.77	12.3
Median	12.2	3.89	5.63	11.1
SD	9.93	5.94	8.92	4.20

^a Vc, volume of distribution of the central compartment; Kcp, first-order intercompartmental transfer rate constant from the central to the peripheral compartment; Kpc, first-order intercompartmental transfer rate constant from the peripheral to the central compartment; CL, total clearance.

TABLE 3. Variance-covariance matrix for pharmacokinetic parameters^a

Parameter	Variance or covariance			CL
	Vc	Kcp	Kpc	
Vc	98.6			
Kcp	9.80	35.3		
Kpc	23.9	-3.33	79.6	
CL	-1.47	2.05	-9.68	17.6

^a Vc, volume of distribution of the central compartment; Kcp, first-order intercompartmental transfer rate constant from the central to the peripheral compartment; Kpc, first-order intercompartmental transfer rate constant from the peripheral to the central compartment; CL, total clearance.

3. The overall fit of the model to the data was good, with the line of best fit for the regression after the Bayesian step being as follows: observed = $1.023 \times \text{predicted} + 0.262$; $r^2 = 0.919$; $P \ll 0.001$. Measures of bias and precision were acceptable at -0.256 mg/liter and $1.982 \text{ (mg/liter)}^2$, respectively. The plot is presented in Fig. 2.

Analysis of covariates. When we studied the influence of covariates on imipenem clearance, the covariates of age, weight, height, and body surface area all remained in the model. These covariates explained 88.8% of the variance in imipenem clearance. Breakpoints were identified in all covariates with CART analysis. CART analysis is a recursive partitioning algorithm. As such, it generates all possible breakpoints in the independent variable and examines the outcomes to see where the differences are most significant. The final CART model, employing only the breakpoints as covariates, had age and body surface area with breakpoints of <46 years and $\geq 1.84 \text{ m}^2$, respectively.

We tried to link different covariates to the probability of death. The model in our logistic regression had the SOFA score as a covariate. This single covariate was highly predictive of the outcome ($P < 0.00004$). A breakpoint was sought in the data using CART analysis. This demonstrated that a SOFA score of <8 was predictive of survival in a logistic regression where this was entered as a dichotomous variable ($P < 0.012$).

Monte Carlo simulation evaluation. The probability-of-target-attainment analyses by MIC are shown in Fig. 3A for in-

FIG. 2. Observed-predicted plot for imipenem for all modes of administration. The line of best fit was determined as follows: observed = $1.023 \times \text{predicted} + 0.262$; $r^2 = 0.919$; $P \ll 0.001$.

A: Intermittent infusions

B: Continuous infusion

FIG. 3. Probability of target attainment for imipenem administered as intermittent 40-min infusions at a dose of 1 g q8h (3 g/day) (A) or as continuous infusion at a dose of 2 g/day (B). We studied the $fT_{>MIC}$ targets of 20%, 30%, and 40% of the dosing interval.

termittent treatment and in Fig. 3B for continuous infusion. Figure 3A shows that intermittent administration of 1 g q8h had a 90% target attainment probability for achieving the target $fT_{>MIC}$ of 20% out to an MIC of 8 mg/liter, while this was 4 mg/liter for the $fT_{>MIC}$ target of 30% and 1 to 2 mg/liter for the $fT_{>MIC}$ target of 40% (88% probability at 2 mg/liter). For continuous infusion (Fig. 3B), all three targets were achieved at the 90% probability level at an MIC of 2 to 4 mg/liter (86% at 4 mg/liter).

For our ICU patients, the coverage generated by both regimens was excellent. The $fT_{>MIC}$ for all recovered pathogens was 100% ($n = 20$), and in most instances, the $fT_{>4 \times MIC}$ was 100%, indicating that maximal organism killing was most likely achieved all the time.

Toxicity evaluation, microbiology, and patient outcome. No imipenem-related adverse reactions (i.e., seizures) were noted during the study. Microbiological specimens taken prior to imipenem treatment revealed, in the continuous-treatment group, *Acinetobacter lwoffii* ($n = 1$), *Escherichia coli* ($n = 1$), *Enterobacter cloacae* ($n = 2$), *Enterobacter gergoviae* ($n = 1$), *Pseudomonas aeruginosa* ($n = 3$), and *Klebsiella pneumoniae* ($n = 2$). For comparison, in the intermittent-treatment group, *E. coli* ($n = 2$), *Enterobacter cloacae* ($n = 1$), *Pseudomonas aeruginosa* ($n = 1$), *Klebsiella pneumoniae* ($n = 3$), *Serratia*

marcescens ($n = 1$), *Proteus mirabilis* ($n = 1$), and *Acinetobacter baumannii* ($n = 1$) were found.

The infecting pathogens in the intermittent-treatment group had an MIC of 0.125 mg/liter or below for six patients, an MIC of 0.25 mg/liter for three patients, and an MIC of 0.5 mg/liter for one patient. The pathogens in the continuous-infusion group had an MIC of 0.125 mg/liter or below for five patients, an MIC of 0.25, 0.5, or 2 mg/liter for one patient each, and an MIC of 1 mg/liter for two patients.

Of the 20 patients, 17 patients survived. There were two deaths in the intermittent-treatment group and one death in the continuous-infusion group. The two patients in the intermittent group who died were infected by *Klebsiella pneumoniae* with an MIC of ≤ 0.125 mg/liter or 0.25 mg/liter. The patient in the continuous-infusion group who died was infected by *Pseudomonas aeruginosa* with an MIC of 1 mg/liter. Two of the three nonsurvivors died from refractory increased intracranial pressure. The third patient was an elderly woman who developed multiple organ failure from abdominal complications that were not treated further, and she died after withdrawal of therapy.

DISCUSSION

We examined the use of imipenem-cilastatin for treatment of seriously infected patients in the ICU. This agent and class of agents have particular utility for therapy of ICU infections, in that emergence of resistance is quite rare during therapy. Organisms can be resistant a priori. This occurs if the organism carries a plasmid with a carbapenem-hydrolyzing enzyme (e.g., *vim* or *imp* β -lactamases) or this type of enzyme on its chromosome (e.g., *Stenotrophomonas maltophilia*) or if an organism such as an *Enterobacter* or *Pseudomonas aeruginosa* strain has a stably derepressed *ampC*-type enzyme plus a deleted porin. Resistance occurring during therapy is most frequently seen with *Pseudomonas* infections, where *oprD2* is lost (with or without stable derepression), and with *Acinetobacter*. Fortunately, all of these are rare events.

Carbapenems also have a broad spectrum of activity, covering the vast majority of ICU pathogens, except for methicillin-resistant *Staphylococcus aureus* and *Enterococcus faecium*. One of the questions we wished to address was how well two different modes of administration of imipenem-cilastatin would provide coverage for the common ICU pathogens. Therefore, we examined intermittent administration of 1 g q8h (3 g/day) and compared it to a continuous infusion of 2 g/day after a 1-g loading dose. Administration of imipenem by continuous infusion requires additional work to reconstitute imipenem in the infusion solution due to its low solubility compared to other β -lactams. Additionally, imipenem and meropenem are the least stable of the β -lactams studied by Viaene et al. (26). According to the prescribing information (German product information, Zienam; MSD), imipenem solutions are sufficiently stable for 4 h at 25°C. Therefore, we reconstituted 250 mg of imipenem every 3 h (solution stored at 21°C during infusion) for treatment by continuous infusion. Although this requires additional work, we believe that this effort is both feasible for the highly qualified personnel at an ICU unit and justified for a potentially life-saving treatment option for critically ill patients.

The coverage generated by both regimens was excellent. The $fT_{>MIC}$ for all recovered pathogens was 100% ($n = 20$), and in most instances, the $fT_{>4 \times MIC}$ was 100%, indicating that maximal organism killing was achieved all the time. The maximum rate of bacterial killing of β -lactams is often achieved at concentrations of about four to six times the MIC (7). Therefore, achieving the target 100% $fT_{>4 \times MIC}$ might be important for maximum bacterial killing in patients. More studies, e.g., with critically ill patients, are required to further substantiate the target for near-maximal bacterial killing in humans. There are data for six critically ill patients which show a lesser extent of tissue distribution for muscle and subcutaneous tissue and a slower equilibration half-life than those for five healthy volunteers (25). A lesser extent of lung penetration would decrease the probability of target attainment in our study.

Three patients in this study failed therapy and died. For each of these patients, the $fT_{>MIC}$ was 100%, raising the question of why these patients died, since the antimicrobial therapy was near maximal. We examined this question with logistic regression analysis, trying to link different covariates to the probability of death. The final model had only the SOFA score as a highly predictive covariate for outcome ($P < 0.00004$). A SOFA score of < 8 was predictive for survival ($P < 0.012$). This finding is important in that it points out how difficult the therapy for infected patients in the ICU is. Severe physiological malfunctioning can result in failure of therapy for infection even when the drug therapy is optimal.

We also wished to examine the pharmacokinetics of imipenem for infected intensive-care patients. The population pharmacokinetic analysis demonstrated a good fit of the model to the data (see Fig. 2). The imipenem clearance was 12.3 ± 4.20 liters/h. This estimate of clearance is reasonably concordant with estimates of imipenem clearance seen in volunteer studies (16), but our estimate of the population standard deviation is a bit larger, as one would expect for a population that is older (median age, 66 years) and sicker. We did not estimate the between-occasion variability of total clearance in our population pharmacokinetic model, since our sampling schedule was sparse (Fig. 1). Instead, we used analysis-of-variance statistics to compare the between-subject variability and between-occasion variability of observed concentrations for the continuous-infusion group. We found that between-subject variability accounted for about 75% of total variability in the observed concentrations during continuous infusion. This suggests that between-patient variability (35% coefficient of variation) was more important than between-occasion variability (20% coefficient of variation) for achieving a pharmacokinetic/pharmacodynamic target. A between-occasion variability of 20% supports the use of target concentration intervention (11) for imipenem.

The volume of distribution of the central compartment was 12.2 ± 9.93 liters. This value is, again, close to the value seen for healthy volunteers but more variable than that seen for healthy volunteer populations. This is, again, likely due to studying more seriously ill patients.

Since the continuous-infusion mode of administration provided equivalent coverage at two-thirds of the daily dose seen with intermittent administration, we felt it was important to explore the relationship between the patients' demographic covariates and the clearance of imipenem. In the continuous-

infusion situation, the clearance will determine the ultimate steady-state drug concentration and therefore the adequacy of therapy. When we examined this with a general linear model, age, weight, height, and body surface area all remained in the model. Interestingly, estimated creatinine clearance did not significantly influence imipenem clearance. This is probably due to the significant nonrenal clearance of imipenem, represented by formation of an open-lactam metabolite.

All of these covariates also had breakpoint values identified by CART analysis. When these dichotomous variables were examined by a general linear model, only age (≥ 46 years) and body surface area ($\geq 1.84 \text{ m}^2$) remained in the model. Younger patients and larger patients had higher imipenem clearances. The final model had a P value of $\ll 0.001$ and explained 88.8% of the variance ($r^2 = 0.888$). When the age was ≥ 46 years and the body surface area was $< 1.84 \text{ m}^2$, mean imipenem clearance was 8.61 ± 1.76 liters/h versus 14.4 ± 3.90 liters/h for the other patients. When the age was < 46 years and the body surface area was $\geq 1.84 \text{ m}^2$, the imipenem clearance was 18.9 ± 1.62 liters/h versus 10.2 ± 1.92 liters/h for the other patients. Consequently, when a patient is both large in body surface area and young, higher doses of imipenem in continuous-infusion mode should be used.

Finally, we also wished to employ the pharmacokinetic information derived from our infected patients to determine target attainment probabilities for MICs likely to be seen with critically ill patients. In Fig. 3A, we can see that intermittent short-term infusion of 1 g q8h has a 90% target attainment probability for achieving the target $fT_{>MIC}$ of 20% out to an MIC of 8 mg/liter, while this was 4 mg/liter for the $fT_{>MIC}$ target of 30% and 1 to 2 mg/liter for the $fT_{>MIC}$ target of 40% (88% probability at 2 mg/liter). Data from a lung infection model for neutropenic mice (3) show that 20% $fT_{>MIC}$ values are required to achieve bacteriostasis at 24 h and 40% $fT_{>MIC}$ values are required for a drop in bacterial counts by about 2 $\log_{10}$ at 24 h for carbapenems. Since the exact target for imipenem in critically ill patients with nosocomial pneumonia is unknown, we used the target from neutropenic mice. Ambrose et al. (1) found good agreement between targets from animal infection models and data from infected patients. However, more large clinical trials are required to identify the exact targets for β -lactams in ICU patients. For continuous infusion (Fig. 3B), all three targets were achieved at the 90% probability level at an MIC of 2 to 4 mg/liter (86% at 4 mg/liter). This indicates that imipenem-cilastatin provides robust coverage for the most common nosocomial pathogens when administered either in intermittent short-term infusion of 1 g q8h or in a continuous infusion of 2 g per day.

In summary, we examined infected ICU patients given imipenem-cilastatin by two different modes of administration. All patients had an $fT_{>MIC}$ of 100% for their recovered pathogen. Failures were explained by the severity of the physiologic impairment engendered by the infection (SOFA score). The imipenem clearance and volume of distribution were, on average, similar to those seen for healthy volunteers but were more variable. The variability was explained mainly by the age and body surface area of the patient. Finally, Monte Carlo simulation demonstrates that administration of imipenem-cilastatin in either of the modes of administration in this study resulted

in robust empirical coverage for the majority of important nosocomial pathogens.

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