Research Paper

Variability in plasma concentration of cefotaxime in critically ill patients in an Intensive Care Unit of India and its pharmacodynamic outcome: A nonrandomized, prospective, open-label, analytical study

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Received: 10-09-2015 **Revised: 04-11-2015** **Accepted: 03-01-2016**

ABSTRACT

Background: Cefotaxime is a widely utilized cephalosporin in most intensive care units of India. However, no data are available about its pharmacokinetic/pharmacodynamic variability in critically ill patients of the Indian population. **Aim:** To investigate the variability in the plasma concentration and pharmacodynamic profile of intermittent dosing of cefotaxime in critically ill patients, according to their *locus* of infection and causative organism. **Materials and Methods:** Cefotaxime levels were determined using high-performance liquid chromatography by grouping patients according to their *locus* of infection as hepatobiliary, renal, pulmonary, and others. Patients with cefotaxime concentration below the minimum inhibitory concentration (MIC) and 5 times below the MIC for the isolated organism were determined. **Results:** The difference in the plasma cefotaxime concentration between the hepatobiliary and the nonhepatobiliary groups was significant at 1 h (P = 0.02) following drug dosing, while the difference was significant between the renal and nonrenal group at 1 h (P = 0.001), 4 h (P = 0.009), and 8 h (P = 0.02) after drug dosing. The pulmonary group showed significantly (P < 0.05) lower plasma cefotaxime levels than the nonpulmonary group at all-time points. The cefotaxime levels were below the MIC and below 5 times the MIC for the isolated organism in 16.67% and 43.33% of the patients, respectively. **Conclusion:** The concentration of cefotaxime differs according to the *locus* of an infection in critically ill patients. Use of another class of antibiotic or shifting to continuous dosing of cefotaxime, for organisms having MIC values above 1 mg/L, is advisable due to the fear of resistance.

Key words: Antibiotic resistance, intermittent dosing, *locus* of infection, minimum inhibitory concentration, pharmacokinetics

Access this article online	
Quick Response Code:	Website: www.jpharmacol.com
	DOI: 10.4103/0976-500X.179356

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How to cite this article: Abhilash B, Tripathi CD, Gogia AR, Meshram GG, Kumar M, Suraj B. Variability in plasma concentration of cefotaxime in critically ill patients in an Intensive Care Unit of India and its pharmacodynamic outcome: A nonrandomized, prospective, open-label, analytical study. J Pharmacol Pharmacother 2016;7:15-21.

INTRODUCTION

The challenges in managing patients with infection in the Intensive Care Unit (ICU) are increasing in an era where there are dwindling antimicrobial choices for multidrug-resistant pathogens. Cefotaxime is a broad spectrum, third generation semisynthetic cephalosporin, used in most ICUs of India.[1,2] The pharmacokinetics/pharmacodynamics of cefotaxime can be highly variable depending on the clinical situation involved, leading to unpredictable plasma concentrations.[3] In critically ill patients the concentration of cefotaxime could be further altered due to variations in the intravascular volume, vascular permeability, and in the composition and distribution of plasma proteins.[4,5] The presence of hepatic and renal insufficiency can affect its metabolism as well.[6,7]

The dosage regimen of cefotaxime in critically ill patients is based on pharmacokinetic data obtained from healthy and less severely ill patients in the Western population.[8,9] No pharmacokinetic or pharmacodynamic data about cefotaxime is available in critically ill patients of the Indian population despite differences in their genetic pool from the Western population. The emergence of resistant strains of organisms, isolated from Indian ICUs, due to inadequate antibiotic levels achieved has got global implications. Furthermore, there are a very few guidelines available for the dose modification of cefotaxime according to the site of infection. Therefore, the purpose of this study was to evaluate the variability in the concentration of cefotaxime at different time intervals by grouping patients according to their locus of infection as renal, hepatobiliary, pulmonary, and others; and determining the number of patients in which the concentration of cefotaxime was below the minimum inhibitory concentration (MIC) and below 5 times the MIC for the isolated organism. The pharmacokinetic/pharmacodynamic data obtained from the study will enable physicians to optimize the dosage regimen of cefotaxime in critically ill patients of the Indian population, according to the site of the clinical infection and the pathogen involved, so as to limit the risk of suboptimal drug concentration or antibiotic resistance.[10,11]

MATERIALS AND METHODS

Study design and participants

The present study is nonrandomized, prospective, open-label, and analytical in nature and was conducted in the Department of Pharmacology and Medical ICU, Department of Anaesthesia, Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi from January 2012 to March 2013. The study conforms to the guidelines approved by the "Institutional Human Ethics Committee" of Vardhman Mahavir Medical College and to the Helsinki Declaration of 1975, as revised in 2000.

Patients of either sex, 18–70 years of age, admitted to the ICU for any cause receiving cefotaxime as an antibiotic were included in the study after taking a valid written informed consent from the patient/patient party. Patients with grave prognosis as diagnosed by the treating physician owing to lesser turnaround time and patients with creatinine clearance of <20 ml/min were excluded from the study. A total of thirty patients were included in the study. A patient information sheet was provided to all patients.

Cefotaxime administration and blood sampling

The planned duration of cefotaxime administration was 7 days. Cefotaxime 1 g was infused intravenously over a period of 30 min in 3 dosages/day at intervals of 8 h each. The study investigator had no role in choosing the treatment option for the patients, and it was at the discretion of the treating physician. Cefotaxime was discontinued if the isolated microorganism was shown to be resistant.

Blood samples were drawn from the patients after 3 days of starting the cefotaxime therapy. Approximately, 2 ml of blood was withdrawn from the patients through the intravenous route at time points of 1, 2, 4, and 8 h postinfusion, and analyzed within 15 min from the time of blood withdrawal.

For each patient, creatinine clearance was calculated by measuring 12-h urine volume, and urine and plasma creatinine concentrations were determined immediately prior to the beginning of the study.

Drug assay

Cefotaxime concentration in plasma was estimated using high-performance liquid chromatography as described by Jehl *et al*.[12] The separation was done on the analytical column 250 × 4.6 ODS (Waters Corporation, Milford, USA). Ammonium acetate (Sisco Research Laboratories, New Delhi, India) served as buffer and acetonitrile (Fisher Scientific, Loughborough, England) as mobile phase with a flow rate of 1.0 ml/min. Detection of cefotaxime was done at the wavelength of 254 nm using Waters UV2489 detector. Cefotaxime (Savior Lifetech Corporation, Chunan Chen, Taiwan) served as the internal standard. The calibration curve obtained by quadratic regression for the assay was linear over the range of 1–100 μg/ml with a "r^2" value of more than 0.9. The mean retention time observed was approximately 6.78 min. The standard equation obtained was $y = 132.38x - 58.65$. The accuracy was calculated as the percent deviation from the target value and ranged from 3.1% to 5.8% for 3 quality control concentrations (1 μ/ml, 5 μg/ml, 10 μg/ml). The intraday and interday coefficients of variation ranged from 2.2% to 9.5% and 9.5% to 10.5%, respectively, for concentrations ranging from 1 to 100 μg/ml.

Microbiological studies

Antimicrobial susceptibility tests were performed by the disk diffusion method according to the guidelines established by the Clinical and Laboratory Standards Institute, 2009. Blood and site-specific samples, obtained from the patients, were processed by the BACTEC 9240 system (Becton Dickinson Diagnostic Instrument Systems, Towson, USA). If both the blood and site-specific cultures reports were positive, then the blood culture reports were considered for analyses. The MIC for the isolated organisms to cefotaxime was determined using the E-test method (AB Biodisk, Solna, Sweden). In the case of polymicrobial infections, the organism with the highest MIC was considered for analyses.

Cefotaxime concentration and pharmacodynamic parameters

The patients were grouped according to their *locus* of infection as hepatobiliary, renal, pulmonary, and others. The plasma concentration of cefotaxime in the hepatobiliary, renal, and pulmonary groups was compared with that of the total number of patients included in the study other than that of the group being compared with.

The patients with cefotaxime concentration below the MIC and below 5 times the MIC for the microorganism cultured from each patient were calculated at time points of 1, 2, 4, and 8 h after drug administration.

Statistical analysis

All the parameters were analyzed by using SPSS 20.0 version (IBM Corporation, New York, USA). Statistical comparison between various subgroups within the main group was carried out by the Mann–Whitney U-test. All the results are presented as mean ± standard deviation (SD) unless otherwise specified. $P < 0.05$ was considered statistically significant. Assuming an α error of 5% and a power of 70%, with a true difference of 0.2 mg/L in the trough concentration of cefotaxime, 8 h following drug administration, between the two groups and a SD of 0.20, the sample size was calculated to be 6 in each arm.

RESULTS

Patient characteristics

Patient characteristics are shown in Table 1. There were 2 mortalities, one due to *Escherichia coli* infection and the other due to *Staphylococcus aureus* infection. Remaining patients recovered with the course of time on treatment. Weight versus plasma concentration of cefotaxime at 1, 2, 4, and 8 h intervals did not show any significant correlation.

Table 1: Patient characteristics

Characteristics	Values
Total number of patients	30
Age (years) (mean, range)	43.5 (22-82)
Gender (%)	Males: 20 (66.7)
	Females: 10 (33.3)
Mean weight (kg)±SD (range)	64.33±11.26 (43-85)
Creatinine clearance (range) (ml/min)	31-179
Diabetes mellitus (%)	7 (23.33)
Hypertension (%)	9 (30)
Site of infection	
Hepatobiliary	7
Renal	6
Pulmonary	6
Others	11

SD=Standard deviation

Microbiological studies

The microorganisms isolated were *Streptococcus pneumoniae* ($n = 8$), *E. coli* ($n = 7$), *Klebsiella* spp. ($n = 6$), *Salmonella typhi* ($n = 2$), *Proteus* ($n = 2$), Group D *Streptococcus* ($n = 1$), *Streptococcus viridians* ($n = 1$), *S. aureus* ($n = 1$), *Staphylococcus epidermidis* ($n = 1$), and *Haemophilus influenzae* ($n = 1$) [Table 2].

Cefotaxime concentration and pharmacodynamic parameters

The plasma concentration of cefotaxime between the hepatobiliary and the nonhepatobiliary groups was statistically significant at 1 h after cefotaxime dosing ($P = 0.02$) while that between the renal and the nonrenal groups was statistically significant at time points of 1 h ($P = 0.005$), 4 h ($P = 0.009$), and 8 h ($P = 0.02$) after drug administration and the plasma cefotaxime concentration values of the pulmonary and the nonpulmonary groups when compared were found to be statistically significant at time points of 1 h ($P = 0.01$), 2 h ($P = 0.002$), 4 h ($P = 0.006$) and 8 h ($P = 0.005$) after cefotaxime dosing [Table 3].

Cefotaxime concentration exceeded the MIC for most of the pathogens isolated except for *Klebsiella* spp. ($n = 3$), *S. aureus* ($n = 1$) and *H. influenzae* ($n = 1$). Except for six patients infected with *Klebsiella* spp., three patients infected with *S. pneumoniae*, two patients infected with *Proteus,* one patient infected with *S. aureus*, and one patient infected with *H. influenzae*, all patients had cefotaxime levels above 5 times the MIC for the causative organism (indicating optimum bacterial killing ability) [Table 4].

DISCUSSION

Antibiotics have played a major role since the last 60 years in saving lives of millions of people. With cefotaxime being the one of the commonly used antibiotics in the ICU setup, there is a compelling need to get the treatment protocols right, keeping in mind the clinical situation of patients, to prevent further development of antibiotic resistance and reducing the economic burden on the patient.

Table 2: Microbiological samples according to the diagnosis

Diagnosis	Samples collected	Samples positive	Organisms isolated†
Hepatobiliary cases (7)	Blood (7)	7	*Klebsiella* spp. (3)
Acute cholangitis with gall stones (3)			*E. coli* (3)
Acute bacterial hepatitis (2)			*S. aureus* (1)
Hepatic abscess (2)			
Renal cases (6)	Blood (6)	2	*E. coli* (3)
Complicated urinary tract infections (6)	Midstream urine (3)	2	*Proteus* (2)
	Catheter tip (3)	3	*Klebsiella* spp. (1)
Pulmonary cases (6)	Blood (6)	3	*S. pneumonia* (4)
Community-acquired pneumonia (3)	Sputum (8)	2	*Klebsiella* spp. (1)
Chronic obstructive pulmonary disease (1)	Bronchoalveolar lavage (1)	1	*H. influenzae* (1)
Ventilator-associated pneumonia (2)			
Others (11)	Blood (11)	6	*S. pneumonia* (4)
Complicated gastroenteritis (2)	Surface swab (3)	4	*S. typhi* (2)
Suppurative peritonitis (2)	Stool (2)	2	*Klebsiella* spp. (1)
Diabetic foot with cellulitis (2)			*E. coli* (1)
Septic arthritis (2)			*S. viridians* (1)
Spontaneous bacterial peritonitis (1)			*S. epidermitidis* (1)
Intravenous catheter-induced sepsis (1)			Group D *Streptococcus* (1)
Infected surgical wound (1)			

Values in parenthesis represent "*n*". †If both the site-specific and blood culture reports were positive, and then the organism isolated in the blood culture was considered for analyses. *S. epidermiditis=Staphylococcus epidermidis, H. influenzae=Haemophilus influenzae, S. aureus=Staphylococcus aureus, S. typhi=Salmonella typhi, E. coli=Escherichia coli, S. viridians=Streptococcus viridians; S. pneumonia=Streptococcus pneumonia*

Table 3: Plasma concentration of cefotaxime according to the site of infection at various time points

	Cefotaxime concentration (mg/L)			
Groups	**1 h**	**2 h**	**4 h**	**8 h**
Hepatobiliary (*n*=7)	19.04±1.24*[a]	8.09±0.85	2.73±0.47	1.11±0.38
Nonhepatobiliary (*n*=23)	17.49±1.33*[a]	7.43±0.58	2.55±0.34	1.00±0.21
Renal (*n*=6)	19.11±0.76*[b]	7.90±0.46	2.93±0.30*[b]	1.19±0.15*[b]
Nonrenal (*n*=24)	17.54±1.42*[b]	7.51±0.73	2.51±0.35*[b]	0.98±0.26*[b]
Pulmonary (*n*=6)	16.13±0.52*[c]	6.88±0.36*[c]	2.29±0.25*[c]	0.79±0.18*[c]
Nonpulmonary (*n*=24)	18.29±1.42*[c]	7.76±0.65*[c]	2.67±0.36*[c]	1.08±0.24*[c]

Mann–Whitney U-test. Values are the mean±SD. *[a]$P<0.05$, when the hepatobiliary group is compared to the nonhepatobiliary group. *[b]$P<0.05$, when the renal group is compared to the nonrenal group, *[c]$P<0.05$ when the pulmonary group is compared to the nonpulmonary group. SD=Standard deviation

Table 4: Plasma cefotaxime concentration below minimum inhibitory concentration and below 5 times minimum inhibitory concentration for the isolated organism

Organism	*n*	Range/mean±SD of MIC for the organism (mg/L)	Cefotaxime concentration (mean±SD in mg/L) at different time points				Patients with cefotaxime concentration <MIC	Patients with cefotaxime concentration <5 times MIC
			1 h	2 h	4 h	8 h		
S. pneumoniae	8	0.06-0.25 (0.16±0.07)	16.62±0.98	7.15±0.74	2.34±0.24	0.89±0.23†	0	3
E. coli	7	0.09-0.25 (0.17±0.09)	18.47±1.45	7.51±0.48	2.71±0.43	1.05±0.23	0	0
Klebsiella spp.	6	1.00-1.50 (1.25±0.27)	18.56±1.95	8.26±0.87	2.84±0.45†	1.21±0.36*,†	3	6
S. typhi	2	0.05-0.19 (0.12±0.10)	18.05±0.14	7.58±0.18	2.55±0.48	0.99±0.06	0	0
Proteus	2	0.38-0.50 (0.44±0.08)	18.20±0.35	7.63±0.18	2.58±0.11	1.00±0.03†	0	2
Group D *Streptococcus*	1	0.13±0.00	17.84±0.00	7.50±0.00	2.42±0.00	0.96±0.00	0	0
S. viridians	1	0.13±0.00	17.30±0.00	7.35±0.00	2.65±0.00	0.85±0.00	0	0
S. aureus	1	1.50±0.00	19.44±0.00	8.20±0.00	3.00±0.00†	1.30±0.00*,†	1	1
H. influenzae	1	1.00±0.00	16.70±0.00	7.00±0.00	2.30±0.00†	0.72±0.00*,†	1	1
S. epidermiditis	1	0.09±0.00	18.23±0.00	7.81±0.00	2.54±0.00	1.22±0.00	0	0

*Cefotaxime plasma concentration below the MIC for the isolated organism, †Cefotaxime plasma concentration below 5 times the MIC for the isolated organism. MIC=Minimum inhibitory concentration, *S. viridians=Streptococcus viridians, S. epidermiditis=Staphylococcus epidermidis, H. influenzae=Haemophilus influenzae, S. aureus=Staphylococcus aureus, S. typhi=Salmonella typhi, E. coli=Escherichia coli, S. pneumonia=Streptococcus pneumonia*, SD=Standard deviation

Thirty patients were enrolled in the study of which 67% were males. The probable reason for a higher male to female ratio is the fact that in the Indian scenario, female populations are reluctant to utilize hospital care facilities even if they are critically ill.[13]

Comparison of the weight of the patients (64.33 ± 11.26 kg) with the plasma concentration of cefotaxime (1, 2, 4, and 8 h) did not reveal any significant correlation, indicating that treatment protocol for these infectious

conditions should be based only on the clinical severity of the patients.[14]

The most common organisms isolated in patients treated with cefotaxime were *S. pneumoniae* and *E. coli.* In an earlier study conducted in Indian ICUs, *E. coli* was the commonest organism isolated followed by *Klebsiella* spp.[15]

The plasma concentration of cefotaxime in the hepatobiliary group was significantly lower than the patients in the nonhepatobiliary group at the time point of 1 h after drug administration. This observation may be misleading due to the low confidence intervals (<20%). A previous study concluded that there was no significant variation of the cefotaxime plasma concentration in patients with hepatic dysfunction, and any variation could have been directly or indirectly related to the extent of renal function rather than the reduced metabolic activity of the liver.[16]

Analysis of plasma concentration of cefotaxime in patients between renal and nonrenal groups revealed a significant difference at time points of 1, 4, and 8 h after dosing. A previous study showed that with a significant decline in the renal creatinine clearance (<20 ml/min), the plasma concentration of cefotaxime increased over time at all dosing intervals.[17] In this study, the creatinine clearance levels in the six patients with renal infections ranged from 31 to 44 ml/min, as compared to the 24 patients with nonrenal infections where the minimum creatinine clearance was 78 ml/min. The difference in the plasma concentration of cefotaxime at the time points of 1, 4, and 8 h could have been due to varying creatinine clearance in the study group. However, since the sampling schedule was sparse in the present study, the between-occasion variability of creatinine clearance could not be estimated. From these observations, it can be suggested that patients with creatinine clearance between 30 and 45 ml/min should be carefully monitored for signs of an increase in plasma cefotaxime concentration so as to prevent worsening of the renal failure indices.

Cefotaxime plasma concentration in patients with pulmonary infections when compared to patients with nonpulmonary infections at 1, 2, 4, and 8 h after dosing showed a significant difference at all the time points. This observation was in conflict with another study conducted in the Japanese population wherein patients undergoing lung surgery showed relatively no significant difference in the mean concentrations of cefotaxime in the blood and lung tissue biopsy.[18] Nevertheless, direct comparative studies similar to the present study are lacking. In this study, which included the Indian population, there may be a possibility of active sequestration of cefotaxime in the lung tissue of patients with pulmonary infections, thus causing a significant decrease in the plasma concentration of cefotaxime. However, due to the drawback of low confidence intervals (<20%) in the present study this observation needs further evaluation. Confounding factors in terms of comorbidities, varying renal clearance, causing altered levels of plasma cefotaxime cannot be ruled out either.

Plasma concentration of an antibiotic above the MIC value for the isolated organism is one of the pharmacodynamic outcome predictors of antibiotic efficacy.[19] If the antibiotic level falls below the MIC level, new bacterial growth will occur. This could decrease the efficacy of the antibiotic and increase the risk of antibiotic resistance.[20] In addition, maximum bacterial killing rates may be achieved only at concentrations 4 or 5 times the MIC for the isolated pathogen.[21,22] In the present study, the concentration of cefotaxime was below the MIC and below 5 times the MIC for the isolated organisms in 16.67% (5/30) and 43.33% (13/30) of the patients, respectively. A previous study had reported similar findings wherein 40% (8/20) and 65% (13/20) of the patients, treated with intermittent dosing of cefotaxime, had drug levels below the MIC and below 5 times the MIC for the isolated organism, respectively, without the occurrence of any deaths.[14] In this study, out of the five patients having drug levels below the MIC, one patient with *S. aureus* infection died. This death could have been due to antibiotic failure. However, the total numbers of patients with *S. aureus* infection were not substantial enough so as to ascertain this reasoning. Second, the presence of other risk factors attributing to the death of the patient cannot be ruled out either.

The other patients infected with *S. penumoniae*, *Proteus, Klebsiella* spp., and *H. influenzae*, having drug levels below the MIC or below 5 times, the MIC recovered with the course of therapy despite the fact that they were exposed to a risk of antibiotic failure. The emergence of various resistant strains of *Klebsiella* spp., *E. coli* is a problem of global implications hence it is alarming when intermittent dosing of cefotaxime does not achieve the desired MIC levels in an ICU setup of India, wherein the antibiotic resistance rates are higher.[23] There is a concern that clinical outcome for these patients may not be the same due to the evolving mechanisms of antibiotic resistance.

The second death observed in the study was of a patient infected with *E. coli* who had cefotaxime concentration above the MIC and 5 times the MIC for *E. coli* and can be considered as an exception as all other patients with *E. coli* infection recovered after cefotaxime treatment.

After analyzing the above findings, it can be suggested that it is advisable to treat patients admitted to an ICU infected with *S. aureus, S. pneumoniae, H. influenzae, Proteus, Klebsiella* spp., and organisms having an MIC value above 1 mg/L with a different class of antibiotic. Another approach would be to switch from intermittent dosing to continuous dosing of

cefotaxime so as to attain drug levels above the MIC and 5 times the MIC for the isolated pathogen. A drawback of the present study is that the time above MIC, an important pharmacodynamic parameter for time-dependent antibiotics, was not calculated which could have shed further light on the efficacy of the intermittent dosing regimen of cefotaxime.

Despite maintaining optimal antibiotic concentrations in critically ill patients severe physiological derangements can result in the failure of therapy. The 3 major independent risk factors associated with death in ICUs are the presence of central nervous system failure, cardiovascular failure, and acute kidney failure.[24] High sepsis-related organ failure assessment and Acute Physiology and Chronic Health Evaluation II scores are also associated with poor clinical outcomes in critically ill patients with sepsis.[25] Confounding factors such as the presence of preexisting comorbidities, immune suppression, malnutrition, prolonged length of ICU stay, and type/severity of the infection are also important determinants of patient survival in ICUs.[26] Hence, failure of antibiotic therapy may not always be associated with low plasma concentrations or antibiotic resistance. Linking each covariate with the probability of death by logistic regression analysis may partially help in identifying the cause for the adverse clinical outcome in critically ill patients.[25]

CONCLUSION

The concentration of cefotaxime differs according to the *locus* of an infection in critically ill patients. A considerable and consistent decrease in the plasma cefotaxime levels in patients with pulmonary infections was noted hence an escalation in the dose may be required in these cases. All patients on cefotaxime therapy with creatinine clearance of <45 ml/min should be monitored carefully for signs of worsening of renal failure indices. Intermittent dosing of cefotaxime at a dose of 3 g/day may not be adequate so as to achieve a concentration for producing optimal bacterial killing rates in an Indian ICU. However, it would be advisable to use a different class of antibiotic or shift to continuous dosing of cefotaxime for pathogens having MIC values above 1 mg/L.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest

REFERENCES

1. William AP. Penicillins, cephalosporins and other beta lactam antibiotics. In: Brunton L, editor. Goodman and Gilman's the Pharmacolgical Basis of Therapeutics. New York: McGraw Hill; 2011. p. 1146-51.
2. Thomas P, Daly S, Misan G, Steele T. Comparison of the efficacy and adverse effect profile of cefotaxime and ceftriaxone in ICU patients with susceptible infections. Diagn Microbiol Infect Dis 1992;15:89-97.
3. Deck DH, Winston LG. Beta-lactam and other cell wall and membrane active antibiotics. In: Katzung BG, Masters SB, Trevor AJ, editors. Basic and Clinical Pharmacology. New York: McGraw-Hill; 2011. p. 806-1245.
4. Joynt GM, Lipman J, Gomersall CD, Young RJ, Wong EL, Gin T. The pharmacokinetics of once-daily dosing of ceftriaxone in critically ill patients. J Antimicrob Chemother 2001;47:421-9.
5. Garot D, Respaud R, Lanotte P, Simon N, Mercier E, Ehrmann S, *et al.* Population pharmacokinetics of ceftriaxone in critically ill septic patients: A reappraisal. Br J Clin Pharmacol 2011;72:758-67.
6. Ko RJ, Sattler FR, Nichols S, Akriviadis E, Runyon B, Appleman M, *et al.* Pharmacokinetics of cefotaxime and desacetylcefotaxime in patients with liver disease. Antimicrob Agents Chemother 1991;35:1376-80.
7. Doluisio JT. Clinical pharmacokinetics of cefotaxime in patients with normal and reduced renal function. Rev Infect Dis 1982;4 Suppl:S333-45.
8. van Dalen R, Vree TB. Pharmacokinetics of antibiotics in critically ill patients. Intensive Care Med 1990;16 Suppl 3:S235-8.
9. Esmieu F, Guibert J, Rosenkilde HC, Ho I, Le Go A. Pharmacokinetics of cefotaxime in normal human volunteers. J Antimicrob Chemother 1980;6:83-92.
10. Gandhi TN, DePestel DD, Collins CD, Nagel J, Washer LL. Managing antimicrobial resistance in intensive care units. Crit Care Med 2010;38(8 Suppl):S315-23.
11. Pea F, Viale P, Furlanut M. Antimicrobial therapy in critically ill patients: A review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin Pharmacokinet 2005;44:1009-34.
12. Jehl F, Birckel P, Monteil H. Hospital routine analysis of penicillins, third-generation cephalosporins and aztreonam by conventional and high-speed high-performance liquid chromatography. J Chromatogr 1987;413:109-19.
13. Biswal S, Mishra P, Malhotra S, Puri GD, Pandhi P. Drug utilization pattern in the intensive care unit of a tertiary care hospital. J Clin Pharmacol 2006;46:945-51.
14. van Zanten AR, Oudijk M, Nohlmans-Paulssen MK, van der Meer YG, Girbes AR, Polderman KH. Continuous vs. intermittent cefotaxime administration in patients with chronic obstructive pulmonary disease and respiratory tract infections: Pharmacokinetics/pharmacodynamics, bacterial susceptibility and clinical efficacy. Br J Clin Pharmacol 2007;63:100-9.
15. Patwardhan RB, Dhakephalkar PK, Niphadkar KB, Chopade BA. A study on nosocomial pathogens in ICU with special reference to multiresistant *Acinetobacter baumannii* harbouring multiple plasmids. Indian J Med Res 2008;128:178-87.
16. Wise R, Wright N. The pharmacokinetics of cefotaxime and ceftriaxone in renal and hepatic dysfunction. Infection 1985;13 Suppl:S145-50.
17. Matzke GR, Abraham PA, Halstenson CE, Keane WF. Cefotaxime and desacetyl cefotaxime kinetics in renal impairment. Clin Pharmacol Ther 1985;38:31-6.
18. Morita J, Hamaguchi N, Yoshizawa K, Niki S, Kondo K. Study on cefotaxime in respiratory surgery: Transfer to lung tissue and kinetics in serum. Jpn J Antibiot 1989;42:2406-11.
19. Vogelman B, Gudmundsson S, Leggett J, Turnidge J, Ebert S, Craig WA. Correlation of antimicrobial pharmacokinetic parameters with therapeutic efficacy in an animal model. J Infect Dis 1988;158:831-47.
20. Craig WA. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clin Infect Dis 1998;26:1-10.
21. Mouton JW, den Hollander JG. Killing of *Pseudomonas aeruginosa* during continuous and intermittent infusion of ceftazidime in an *in vitro* pharmacokinetic model. Antimicrob Agents Chemother 1994;38:931-6.
22. MacGowan AP. Elements of design: The knowledge on which we build. Clin Microbiol Infect 2004;10:6-11.
23. Brink AJ, Coetzee J, Clay CG, Sithole S, Richards GA, Poirel L, *et al.*

Emergence of New Delhi metallo-beta-lactamase (NDM-1) and *Klebsiella pneumoniae* carbapenemase (KPC-2) in South Africa. J Clin Microbiol 2012;50:525-7.
24. Mayr VD, Dünser MW, Greil V, Jochberger S, Luckner G, Ulmer H, *et al.* Causes of death and determinants of outcome in critically ill patients. Crit Care 2006;10:R154.
25. Sakka SG, Glauner AK, Bulitta JB, Kinzig-Schippers M, Pfister W, Drusano GL, *et al*. Population pharmacokinetics and pharmacodynamics of continuous versus short-term infusion of imipenem-cilastatin in critically ill patients in a randomized, controlled trial. Antimicrob Agents Chemother 2007;51:3304-10.
26. Fish DN. Antimicrobials in chemotherapy strategy. In: Vincent JL, Abraham E, Moore FA, Kochanek PM, Fink MP, editors. Textbook of Critical Care. Philadelphia, PA: Elsevier Saunders; 2011. p. 921-9.