# Pharmacokinetics of Antibiotics or Antifungal Drugs in Intensive Care Units

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Intensive care unit (ICU) patients present several unusual pharmacokinetic (PK) characteristics compared with less seriously ill patients, including increased distribution volume and variable clearance. Interpatient PK variability is often considerable and can produce a wide range of values for PK parameters and major differences in drug exposure. These analyses have led to the development of simulation techniques and population PK models to assess dosing regimens in specific patient subsets. Plasma concentrations may frequently overestimate target-site concentrations and therefore clinical efficacy. The unbound drug concentration at the infection site should be preferred. Although renal replacement therapy techniques are commonly used in ICU patients, data concerning antibiotic dosing in this setting remain limited. Administration of antibacterial agents by continuous infusion is becoming a common technique to avoid undesirable high peak concentrations and low trough concentrations and to optimize PK-pharmacodynamic indices.

## Introduction

Despite many publications devoted to the pharmacokinetic (PK) parameters of anti-infective agents, this issue has been insufficiently addressed in critically ill patients. Until recently, the in vitro susceptibility of microorganisms, and more specifically the minimum inhibitory concentration (MIC), was considered the only essential aspect for antibiotic efficacy in treating severe infections. The relevance of pharmacokinetic-pharmacodynamic (PK-PD) relationships in optimizing drug exposure has been progressively highlighted [1••]. Adequate treatment of severe infections requires optimal PK-PD exposure at the infection site. The PK characteristics may confirm optimal exposure when treating infection with fixed, standard dosing regimens of antimicrobials; conversely, in other instances, PK factors may suggest the need for an adjusted dosage regimen. Consequently, treatment failure in ICU patients may be directly related to failure to achieve target PK parameters at the infection site. Considerable advances have been made in understanding PK issues of anti-infective agents in ICU patients. This review offers a broad perspective on these developments with relevance to clinicians.

## PK Parameters in ICU Populations

Comorbidities, organ dysfunctions, and medical and surgical interventions often modify PK parameters and consequently plasma and tissue drug concentrations. ICU patients present several unusual PK characteristics compared with less seriously ill patients or healthy volunteers, including increased volume of distribution (VD) and variable clearance (CL), making it difficult to achieve therapeutic targets. PK studies therefore should include patients with higher or lower exposure due to differences in drug clearance, to portray more realistically the effects of these potential differences. In recent years, simulation techniques have been used to evaluate antimicrobial dosing regimens from specific subsets of ICU patients. Despite criticisms related to the small numbers of patients included, useful conclusions can be drawn from these studies [2,3]. These results obviously cannot be applied to all ICU populations (eg, morbidly obese or pediatric patients), but they represent a major advance in understanding PK parameters of ICU patients. These parameter estimates and measures of dispersion provide physicians with useful tools in choosing dose and frequency of administration of anti-infective agents. These analyses have led to the development of population PK models in ICU patients with various agents, such as piperacillin [4], cefepime [3], cefpirome [5], ertapenem [6], imipenem [7•], meropenem [8], vancomycin [9], teicoplanin [10], linezolid [10], levofloxacin [11], ciprofloxacin [12], and caspofungin [13•].

## Interpatient Variability and Variability Over Time

Mean PK parameter estimates are commonly used to describe the PK profile of a given antimicrobial. However, this approach does not account for interpatient PK variability, which is often considerable in ICU patients. In a group of ICU patients receiving ceftazidime, a 37% decrease in the volume of the central compartment and a 48% decrease in CL were observed compared with healthy volunteers, with a 50% interpatient variation [2]. Similar findings were reported with linezolid [14]. Interpatient PK variability is often considerable, and can produce a wide range of values for PK parameters and major differences in drug exposure in and between individual patients. In a group of patients receiving ertapenem for ventilator-associated pneumonia (VAP), a two- to threefold variation was observed for peak concentration ($C_{max}$), VD, area under the curve (AUC), half-life ($T_{1/2}$), and CL [15]. Similar results were reported for teicoplanin [16•], cefepime [17], ceftazidime [18], levofloxacin [11], linezolid [14], and colistin [19]. This variability raises questions about the appropriateness of the dose regimen administered, with a frequent risk of underdosage, and justifies monitoring the agent as frequently as possible.

In a specific family of antimicrobial agents, PK characteristics can differ from one agent to another, as illustrated by comparing imipenem and meropenem in septic patients [20]. The mean $C_{max}$ and AUC for imipenem were twofold higher than for meropenem, whereas the mean VD and mean total CL were 30% to 40% higher for meropenem than for imipenem [20].

For agents mainly distributed in extracellular fluids (eg, aminoglycosides), the VD may increase in critically ill patients as a result of fluid shifts and over the time-course of severe infection. This point was illustrated in a group of ICU patients with septic shock, leading to increased VD and decreased $C_{max}$ of gentamicin until a more stable clinical situation was achieved [21]. Consequently, higher doses than conventionally recommended may be needed to optimize plasma concentrations and to ensure clinical efficacy. In contrast, ciprofloxacin PK in critically ill patients does not change over time, and intra-abdominal sepsis does not alter ciprofloxacin PK parameters to a greater degree than sepsis due to other causes [12]. Similarly, infection severity does not appear to influence linezolid's PK parameters [22].

## Changes in Tissue Diffusion

Tissue concentrations of antibiotics at the target site contribute to their therapeutic effects [1••]. Plasma concentrations may overestimate target site concentrations and therefore clinical efficacy. To investigate this issue in nosocomial pneumonia, a methodologically correct approach may be to detect drug concentration levels in the alveolar lining fluid (ALF) and in alveolar macrophages for extracellular and intracellular pathogens, respectively. For deep tissue infection, the drug concentration in the interstitial space fluid of subcutaneous adipose and intramuscular tissues might reflect adequate tissue diffusion. In septic shock, many factors contribute to the decreased tissue diffusion of antimicrobial agents. Changes in regional blood flow, inflammation response, blood volume (eg, hemorrhage, fluid loading, blood transfusion), and low plasma protein concentration are some parameters that interfere with drug diffusion between plasma and tissue.

Several recent publications, most of them concerning patients treated for pneumonia, illustrate this point. In a group of patients receiving intravenous (IV) gentamicin, 240 mg once daily (mean dose 3.5 ± 0.1 mg/kg), the mean peak antibiotic concentrations reached only 4.24 mg/L in the ALF 2 hours after administration, and the ALF/serum penetration ratio was only 32% [23]. The authors concluded that, in treating VAP in ICU patients, higher doses were required to produce higher peak blood levels and obtain active alveolar concentrations against less sensitive microorganisms. Similar conclusions were obtained with tobramycin (7–10 mg/kg once daily) [24•]. In contrast, adequate concentrations in ALF were obtained in community-acquired pneumonia with IV levofloxacin (500 mg once and twice daily) [25], and in VAP with teicoplanin (12 mg/kg every 12 hours for 2 consecutive days, followed by 12 mg/kg once daily) [16•], ertapenem (1 g once daily) [15], and linezolid (600 mg twice daily) [14].

In other tissues, previous studies demonstrated low concentrations of piperacillin and cefpirome in muscle [26], subcutaneous adipose tissue [26], and interstitial fluid [27]. In a small group of head-injury patients receiving vancomycin at a daily dose of 25 mg/kg (500 mg IV over 60 minutes every 6 hours) [28], vancomycin levels in edematous brain close to a posttraumatic hemorrhage reached a maximum value of only 1.2 mg/L. At plasma concentrations of 10 to 15 mg/L, subcutaneous interstitial levels of 4 to 6 mg/L were obtained, which were considered effective for clinical use [28]. In a group of patients with septic shock, adequate metronidazole concentrations in plasma and muscle tissue against *Bacteroides fragilis* were achieved 30 and 140 minutes after administration of 500 mg IV [29]. In *Candida* peritonitis, low concentrations (0.12 mg/L) of amphotericin B (administered by continuous infusion at a dosage of 0.5–1 mg/kg/d) were reported in peritoneal fluid [30]. In 43% of the study population, amphotericin B was below the detection limit after 2 to 4 days of treatment [30]. In the same study, the authors reported adequate peritoneal concentrations of flucytosine similar to those reported in plasma [30].

## Protein Binding

Recent studies have emphasized the importance of unbound drug concentrations. Only the unbound antibiotic concentrations in interstitial fluid at the target site are responsible for the antibacterial effect and may be more relevant in predicting therapeutic efficacy than plasma concentrations. Because most infections occur not in plasma but in tissue sites and their extracellular fluid, the ability of anti-infective agents to reach the target sites is a key determinant of clinical outcome. The distribution of anti-infective agents in plasma and tissue depends on their physical and chemical properties. The difference between total plasma concentrations and free tissue concentrations can be significant in high protein binding of the antibiotic. Therefore, the total plasma concentration is not an ideal PK parameter for rational dosing of antibiotics, and the unbound drug concentration at the infection site should be preferred.

Low plasma protein concentration, and especially low albumin concentration, is almost constantly observed in critically ill patients (eg, due to high fluid loading, hemorrhage, inflammation) [6]. These metabolic changes affect PK parameters such as VD, tissue diffusion, or drug elimination, especially during renal replacement therapy. This issue was illustrated in a study focusing on PK parameters of ceftriaxone, a β-lactam with concentration-dependent albumin binding [31]. Compared with healthy volunteers, ICU patients with iatrogenic hypoalbuminemia have higher free ceftriaxone concentrations during the 24 hours after antibiotic administration. The area under the free ceftriaxone concentration-time curve was twofold higher in patients than in healthy volunteers. Moreover, the free ceftriaxone concentration remained higher than 4 mg/L for a longer time in ICU patients [31]. Similarly, the albumin concentration has a significant impact on caspofungin trough concentrations [13•] and vancomycin clearance [9].

The issue of protein binding and diffusion at the target site can determine drug selection. In ICU patients with VAP, unbound teicoplanin concentrations in serum and ALF were higher than 2 mg/L in all patients with a fraction of free agent unbound to serum proteins ranging from 8% to 42% [16•], whereas unbound ertapenem concentrations in serum and ALF exceeded the $MIC_{90}$ values of most of the causative pathogens encountered in early-onset VAP 50% to 100% of the time [15]. In a cohort of patients with sepsis or septic shock, unbound linezolid fractions ranged from 73% to 95.9% with good distribution in interstitial space fluid of subcutaneous adipose tissue and intramuscular tissue, but with high interindividual variability [32]. Based on the model-predicted unbound concentrations in interstitial space fluid, a more frequent daily dosing regimen of linezolid could be considered for some critically ill patients to avoid subinhibitory unbound concentrations in infected tissue [32].

## Renal Failure and Renal Replacement Therapy

Renal failure is a frequent issue in septic and critically ill patients. Renal replacement therapy techniques are commonly used to treat ICU patients with acute or chronic renal failure. Continuous renal replacement therapy (CRRT) has been widely used in the past decade due to its good hemodynamic tolerance in unstable patients and its efficacy to remove fluid and drugs for a prolonged period (24–48 hours) [33]. Data provided by conventional intermittent hemodialysis (IHD) cannot be accurately extrapolated to CRRT because of the continuous nature of the procedures, differences in membranes used, and differences in blood, ultrafiltrate, and dialysate flow rates. Until recently, only limited published data were available concerning antibiotic dosing during CRRT in critically ill patients [33].

A major difficulty when interpreting these publications relates to the variety of techniques applied. The general principles of drug and solute elimination are based on convection in continuous venovenous hemofiltration (CVVH), diffusion gradients through countercurrent dialysate flow in continuous venovenous hemodialysis (CVVHD), or a combination of diffusive and convective solute transports in continuous venovenous hemodiafiltration (CVVHDF) [33]. CVVHDF can require large volumes of fluid to replace losses during ultrafiltration. Drug removal depends on several technical factors (eg, blood and dialysate flow rates), which are not always clearly presented in publications. Changes in flow rates modify the transmembrane pressure and increase drug clearance. The dialysate concentration may also affect drug removal in hemofiltration. The degree of drug removal by CRRT is proportional to the membrane pore size, usually expressed as a sieving coefficient [33]. The large pores of biosynthetic membranes allow removal of drugs with a larger molecular weight, unlike conventional filters. Protein binding is another important issue. Agents with low protein-binding capacity in serum are more readily removed by CRRT, whereas antibiotics that penetrate and bind to tissues have a larger volume of distribution, reducing the quantity removed during CRRT. Lastly, the variability of antimicrobial dosing and regimens is a parameter to consider in understanding publications.

A comprehensive literature review provides general recommendations for critically ill patients receiving CRRT and describes the most important recent results with the anti-infective agents administered in this setting [33]. Several papers have reported additional progress in this field. Previous studies addressing the PK characteristics of ceftazidime in critically ill patients receiving CRRT were performed with intermittent infusions of the agent. In a group of patients who required CVVHDF, continuous infusion of ceftazidime (2-g IV loading dose and 3-g continuous infusion over 24 hours) demonstrated

satisfactory results [18]. The mean serum ceftazidime steady-state concentration was 33.5 mg/L (range: 28.8–36.3 mg/L). CVVHDF effectively removed continuously infused ceftazidime, with a sieving coefficient of 0.81 ± 0.11 mg/L and CVVHDF clearance of 33.6 ± 4 mg/L [18]. Cefepime (2 g IV every 8 hours) is significantly removed by CVVH and CVVHDF procedures. The total amount of drug removed by hemofiltration was 27.4% of the dose administered, and PK parameters ($T_{1/2}$, VD) differed only slightly from those of previous publications; sieving coefficient was fairly similar (0.76 ± 0.21) [17].

Little information is available concerning linezolid during CRRT. Although several reports have described the use of this drug in patients receiving IHD [34,35], only one case report of CVVHDF [36] and two patients with CVVHF (in another study) [35] have been published. In both reports, mean removal of the drug was low: 8.3% and 12% to 17% of the dose, respectively [35,36].

The PK of colistin methanesulfonate (150 mg every 24 hours, then every 48 hours) and colistin, its metabolite active against *Pseudomonas aeruginosa*, were analyzed in a case report of a patient receiving CVVHDF [37]. CVVHDF clearance of colistin methanesulfonate and colistin were similar (11.2 and 11.9 mL/min, respectively), with removal of 20.3% and 6.8% of the dose in 8 hours, respectively. Consistent with a recent report, serum concentrations of colistin were in the therapeutic range, but fell below the MIC of the *P. aeruginosa* strain in approximately 4 hours [19]. The authors concluded that dosage adjustment should be modest in CVVHDF [37].

Few recent data are available for antifungal agents. In patients with renal failure treated by IHD, the solvent vehicle of the IV form of voriconazole sulphobutylether β-cyclodextrin sodium has an impaired clearance. In four patients receiving voriconazole and undergoing IHD, an accumulation of cyclodextrin sodium was recorded (peak plasma level ranging between 145 and 581 mg/L) without any toxic effect [38]. In critically ill patients without liver cirrhosis undergoing CVVHDF, voriconazole should be given without a dosage adaptation [39]. In a case report of high-volume CVVH, filtration clearance was higher than observed in previous studies with other techniques that might affect the drug's PK [40]. The authors concluded that standard doses can be administered to patients treated by high-volume CVVH, but drug concentrations should be regularly assayed to control efficacy [40]. No information on cyclodextrin sodium removal was available in these two studies.

The advantages of IHD and CRRT were combined recently in a hybrid technique called extended daily dialysis (EDD). EDD for 12 hours per day eliminates as much creatinine and urea as 24 hours of CVVH and could remove drugs to a much greater extent than IHD or CRRT. No published data are available regarding this highly efficient renal replacement therapy's effect on the elimination of frequently used drugs in critically ill patients with renal failure. Moreover, the existing dosing and PK data for patients undergoing either IHD or CRRT may not be applicable to patients treated with EDD because duration, filters used, and blood flow are quite different from the other two techniques.

Moxifloxacin PK in patients undergoing EDD appear similar to those in healthy subjects, and allow treatment with the standard dosage (400 mg/d IV) [41]. Similar conclusions were drawn with moxifloxacin in patients treated by CVVHDF [42]. Levofloxacin, although removed by EDD, has a lower total clearance compared with healthy subjects, suggesting a reduced dosage according to the intensity of renal replacement therapy [41]. One 8-hour EDD treatment removed 18% of meropenem (1 g, 6 hours before EDD) and 26% of vancomycin (1 g, 12 hours before EDD) [43]. Current dosing regimens for these agents run the risk of being significantly underdosed, emphasizing the need for therapeutic drug monitoring when possible [43].

## Prolonged Administration of Antimicrobial Agents

The three most common PK-PD measures to describe antimicrobial therapy efficacy are the duration or percentage of time a drug concentration remains above the MIC (T > MIC or %T > MIC), the ratio of the peak concentration to the MIC ($C_{max}$/MIC), and the ratio of the area under the concentration-time curve at 24 hours to the MIC ($AUC_{0-24}$/MIC). Some antibacterial agents display a time-dependent pattern of bactericidal activity. In this setting, the %T > MIC values for β-lactams or $AUC_{0-24}$/MIC for clindamycin, vancomycin, linezolid, or tigecycline are more closely correlated with efficacy [1••]. This has prompted clinicians to develop dosing strategies that maximize these PK/PD indices, including higher doses, shorter dosing intervals, or prolonged/continuous infusion. Intermittent administration has several drawbacks, such as adverse effects due to undesirable high peak concentrations and low, potentially sub-MIC, trough concentrations. Administration of antibacterial agents by continuous infusion avoids these fluctuations and allows optimization of PK-PD indices [1••]. Several recent studies in ICU patients have used this concept.

Ceftazidime is one of the most frequently prescribed drugs for continuous infusion. A recent study demonstrated that the dose regimen usually recommended (2-g loading dose followed by 3-g/d continuous infusion) is adequate even in CRRT [18]. Recently, a continuous infusion of cefepime (4 g/d) was compared with intermittent administration (2 g/d, twice daily) in combination with amikacin [44]. The AUC was similar in both groups but %T > 5 × MIC was higher in continuous infusion [44]. These results were confirmed in a Monte Carlo simulation with a target free-drug concentration of cefepime

above the MIC (free %T > MIC) for more than 65% of the dosing interval for intermittent administration and continuous infusion [3]. When given as intermittent administration or continuous infusion (0.5-g loading dose followed by 2 or 4 g/d) for *Escherichia coli* or *Klebsiella pneumoniae*, cefepime should achieve the bactericidal target, whereas higher doses (> 4 g/d) were required to achieve the required probability of target attainment for *P. aeruginosa* [3]. Using the same methodology, these authors simulated the free-drug concentrations of cefpirome with the same target for intermittent administration and continuous infusion [5]. When given as intermittent administration or continuous infusion, cefpirome should be successful against *E. coli* and *Klebsiella* spp.., but fails to achieve the bactericidal target against *P. aeruginosa* and *Acinetobacter* spp.., even when administered at high doses (eg, 6 g/d) [5].

Among penicillins, continuous infusion of piperacillin (2-g loading dose followed by 8 g/d) was compared with intermittent administration (4 × 3 g/d) [45]. Mean serum concentrations of piperacillin during continuous infusion remained close to 35 mg/L over the first 48 hours of infusion, and %T > MIC of the pathogens was 100% and 65% of the dosing interval for MICs of 16 and 32 mg/L, respectively [45]. These results were confirmed in a study using piperacillin combined with sulbactam (4/1-g loading dose followed by 8/2 g/d) [46]. Two regimens (12/1.5 g or 16/2 g, after 4/0.5-g loading dose) of piperacillin-tazobactam administered by continuous infusion were compared for the treatment of VAP [47]. A serum piperacillin concentration greater than 35 to 40 mg/L was defined as the bactericidal target. In patients with normal renal function, the high dose of piperacillin/tazobactam (16/2 g) achieved the target concentration, which might not be observed with 12/1.5 g/d. In patients with moderate to advanced renal failure, both dosages achieved serum concentrations well above the threshold of 35 to 40 mg/L [47]. These results are similar to a study evaluating the effect of an extended infusion of piperacillin-tazobactam (3.375 g IV for 4 h every 8 h) compared with intermittent administration (3.375 g IV for 30 min every 4 or 6 hours) for treating *P. aeruginosa* infection [48••]. A Monte Carlo simulation demonstrated that the probability of target attainment (50% free T > MIC) was best achieved with an extended infusion. These results were confirmed in the most severely infected patients, in whom mortality (12.2% vs 31.6%, $P = 0.04$) and length of stay (21 vs 38 days, $P = 0.02$) were decreased compared with intermittent administration regimens [48••].

For the carbapenems, a study compared continuous infusion of imipenem/cilastatin (1-g loading dose followed by 2 g/d) versus intermittent administration (3 × 1 g/d) [7•]. In the continuous infusion group, the average plasma imipenem concentration for all samples between 10 and 70 hours after the start of the first dose was 8.65 ± 3.54 mg/L, and no patient had a plasma concentration below 2 mg/L. Using Monte Carlo simulations with a target 40% free T > MIC, this goal was achieved for 100% of all recovered pathogens. In most instances, the free %T > 4 × MIC was 100%. The probability of target attainment for intermittent administration was greater than 90% up to MICs of 1 to 2 mg/L and 2 to 4 mg/L for continuous infusion [7•].

Recently, intermittent administration of linezolid (600 mg/12 h) was compared with continuous infusion (300-mg loading dose + 900 mg on day 1, followed by 1200 mg/d from day 2) [49]. Following intermittent administration, linezolid trough serum levels ($C_{min}$) varied widely and were below the susceptibility breakpoint (4 mg/L) during the study period; $C_{min}$ was less than 1 mg/L in 50% of patients. Mean serum linezolid levels during continuous infusion were more stable and were always above the susceptibility breakpoint. In addition, free %T > MIC values greater than 85% were more frequent with continuous infusion than with intermittent administration ($P < 0.05$). Finally, continuous infusion led to AUC/MIC values of 80 to 120 more frequently than intermittent administration ($P < 0.05$) [49].

## Conclusions

Most of these results must be confirmed on larger populations and in various infections (eg, intra-abdominal, skin and soft tissue, meningitis, septic shock). The importance of unbound drugs and their concentrations in many tissues must be assessed. The potential benefit of innovative techniques such as continuous infusion on patient outcomes, antibiotic resistance, toxicity, and health care costs needs to be assessed. Although considerable progress has been made in using antibacterial agents, much remains to be done in the administration of antifungal agents.

## Disclosures

No potential conflicts of interest relevant to this article were reported.

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