Pharmacokinetic issues for antibiotics in the critically ill patient

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain principles which influence pharmacokinetics in critically ill patients.
2. Describe rational dosing regimens for antibiotics in critically ill patients.
3. Use this information in a clinical setting.

Dr. Roberts has disclosed that he is the recipient of an education grant to the research center from Astra-Zeneca. Dr. Lipman has disclosed that he is the recipient of an education grant to the research center from Astra-Zeneca; is a consultant/advisor for Astra-Zeneca and Janssen-Cilag; and is on the speaker's bureau for Wyeth Australia.

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Objective: **To discuss the altered pharmacokinetic properties of selected antibiotics in critically ill patients and to develop basic dose adjustment principles for this patient population.**

Data Sources: **PubMed, EMBASE, and the Cochrane-Controlled Trial Register.**

Study Selection: **Relevant papers that reported pharmacokinetics of selected antibiotic classes in critically ill patients and antibiotic pharmacodynamic properties were reviewed. Antibiotics and/or antibiotic classes reviewed included aminoglycosides, β-lactams (including carbapenems), glycopeptides, fluoroquinolones, tigecycline, linezolid, lincosamides, and colistin.**

Data Synthesis: **Antibiotics can be broadly categorized according to their solubility characteristics which can, in turn, help describe possible altered pharmacokinetics that can be caused by the pathophysiological changes common to critical illness. Hydrophilic antibiotics (e.g., aminoglycosides, β-lactams, glycopeptides, and colistin) are mostly affected with the pathphysiological changes observed in critically ill patients with increased volumes of distribution and altered drug clearance (related to changes in creatinine clearance). Lipophilic antibiotics (e.g., fluoroquinolones, macrolides, tigecycline, and lincosamides) have lesser volume of distribution alterations, but may develop altered drug clearances. Using antibiotic pharmacodynamic bacterial kill characteristics, altered dosing regimens can be devised that also account for such pharmacokinetic changes.**

Conclusions: **Knowledge of antibiotic pharmacodynamic properties and the potential altered antibiotic pharmacokinetics in critically ill patients can allow the intensivist to develop individualized dosing regimens. Specifically, for renally cleared drugs, measured creatinine clearance can be used to drive many dose adjustments. Maximizing clinical outcomes and minimizing antibiotic resistance using individualized doses may be best achieved with therapeutic drug monitoring. (Crit Care Med 2009; 37: 840–851)**

KEY WORDS: pharmacokinetics; critically ill; pharmacodynamics; antibiotic; dosing

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Antibiotic treatment of critically ill patients remains a significant challenge to intensivists world-wide with persisting high mortality and morbidity rates. The importance of effective therapy continues to grow with increasing numbers of patients with increasingly levels of sickness severity being admitted to intensive care units (ICUs) (1). Compelling evidence suggests that in infected critically ill patients, source control of the pathogen and early and appropriate antibiotic therapy remains the most important intervention that the clinician can implement for such patients (1–6). Therefore, optimizing antibiotic therapy should be a priority in the management of critically ill patients.

A vast array of pathophysiological changes can occur in critically ill patients that can complicate antibiotic dosing. Knowledge of the pharmacokinetic and pharmacodynamic properties of the antibiotics used for the management of critically ill patients is essential for selecting the antibiotic dosing regimens, which will optimize patient outcomes (7). Changes in volume of distribution (Vd) and clearance (CL) of antibiotics have been noted in these patients, which may affect the antibiotic concentration at the target site. It follows that the pharmacodynamic parameters that determine antibiotic efficacy, which can vary between antibiotic classes, may also be affected. Optimization of these parameters is necessary to maximize the rate of response through patient recovery and minimized antibiotic resistance (7–9).

The aim of this review is to identify the pathophysiological changes that occur in critically ill patients and the effect that they have on the pharmacokinetic behavior, and furthermore, the pharmacodynamic effect of commonly used antibiotics. Furthermore, we seek to develop general principles of dosage adjustment of these antibiotics in critically ill patients. Because of the spectrum of different patient presentations and different levels of organ function that critically ill patients may present with, it is not the intention of this article to provide definitive dose adjustment recommendations for each of the cited antibiotic classes. However, we aim to provide information that empowers the clinician to individualize antibiotic dosing by considering the factors that are most likely to affect antibiotic pharmacokinetics.

Search Strategy and Selection Criteria

Data for this review were identified by searches of PubMed (1966 to February 2008), EMBASE (1966 to February 2008) and the Cochrane Controlled Trial Registry as well as references from relevant articles. Search terms were "antibiotic" or "antibacterial," "intensive care unit," or "critically ill" or "critical illness," and "pharmacokinetics" or "pharmacodynamics." English language papers were reviewed. Numerous articles were identified through searches of the extensive files of the authors. All relevant papers that described antibiotic pharmacodynamics and/or antibiotic pharmacokinetics in critically ill patients were reviewed.

General Concepts

Kill Characteristics of Antibiotics. For antibiotics, pharmacodynamic parameters relate pharmacokinetic parameters to the ability of the antibiotic to kill or inhibit the growth of the infective organism (10). Different antibiotic classes have been shown to have different kill characteristics on bacteria (Fig. 1 and Table 1).

Developing dosing regimens that maximize the rate of response in ICU patients is important for optimizing patient outcomes and minimizing the development of antibiotic resistance (2, 3, 5, 9).

Pharmacokinetic Changes Observed in Critically Ill Patients. The changes to the pharmacokinetic parameters of antibiotics in critically ill patients are driven by both drug and disease factors. From a drug perspective, the hydrophilicity and lipophilicity of the molecule will influence Vd and CL of a drug. Figure 2 summarizes these effects diagrammatically.

Changes in Vd. The pathogenesis of infections in critically ill patients appears highly complex (1, 11–13). Endotoxins from bacteria or fungi may stimulate the production of various endogenous mediators that may affect the vascular endothe-

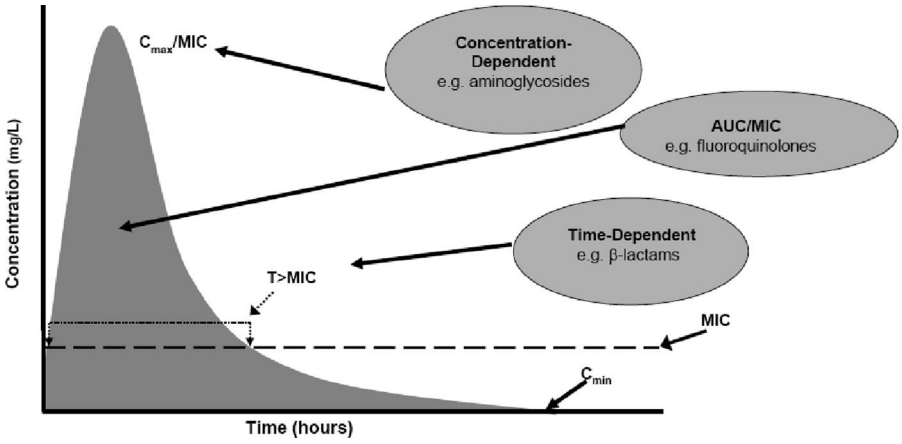

Figure 1. Pharmacokinetic and pharmacodynamic parameters of antibiotics on a concentration vs. time curve. Key: *T > MIC*—The time for which a drug's plasma concentration remains above the minimum inhibitory concentration (MIC) for a dosing period; C_{max}/MIC, the ratio of the maximum plasma antibiotic concentration (C_{max}) to MIC; *AUC*/MIC, the ratio of the area under the concentration time curve during a 24-hour time period (AUC_{0-24}) to MIC.

Table 1. Pharmacodynamic properties that correlate with efficacy of selected antibiotics

Antibiotics	β-lactams Carbapenems Linezolid Erythromycin Clarithromycin Lincosamides	Aminoglycosides Metronidazole Fluoroquinolones Telithromycin Daptomycin Quinupristin/dalfopristin	Fluoroquinolones Aminoglycosides Azithromycin Tetracyclines Glycopeptides Tigecycline Quinupristin/dalfopristin Linezolid
PD kill characteristics	Time-dependent	Concentration-dependent	Concentration-dependent with time-dependence
Optimal PD parameter	T > MIC	C_{max}:MIC	AUC_{0-24}:MIC

MIC, minimum inhibitory concentration; AUC, area under curve; PD, pharmacodynamics; C_{max}, maximum concentration.

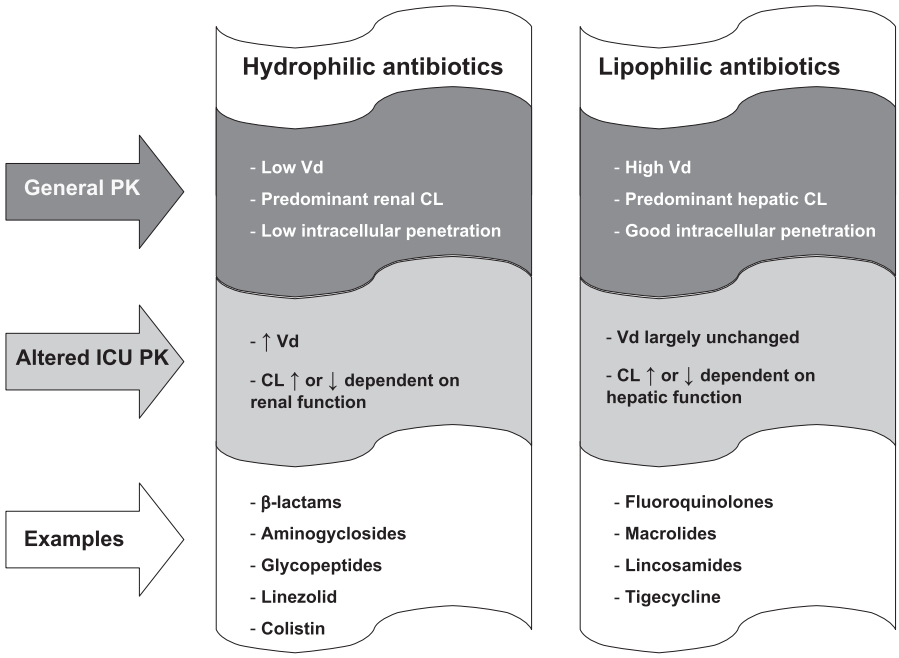

Figure 2. The interrelationship of hydrophilicity and lipophilicty of antibiotic molecules on the pharmacokinetic characteristics in general ward patients (General pharmacokinetics [*PK*]) and the altered PK observed in critically ill patients in intensive care unit (*ICU*). *CL*, clearance; *Vd*, volume of distribution.

lium resulting in either vasoconstriction or vasodilatation with maldistribution of blood flow, endothelial damage, and increased capillary permeability (14). This capillary leak syndrome results in fluid shifts from the intravascular compartment to the interstitial space (15, 16). This would increase the Vd of hydrophilic drugs which decreases their plasma drug concentration. Vd of hydrophilic drugs may also be increased by the presence of mechanical ventilation, hypoalbuminaemia (increased capillary leakage) extracorporeal circuits (e.g., plasma exchange, cardiopulmonary bypass), postsurgical drains, or in patients with significant burn injuries (17–20). Lipophilic drugs typically have a large Vd because of their partitioning into adipose tissue, and as such the increased Vd that results from third-spacing is likely to cause insignificant increases in drug Vd.

Changes in Antibiotic Half-Life. Drug elimination half-life ($T_{1/2}$) is directly related to antibiotic CL and Vd. $T_{1/2}$ is represented by the equation (21):

$$T_{1/2} = \frac{0.693 \times Vd}{CL}$$

It follows that an increased drug CL is likely to reduce $T_{1/2}$, whereas an increased Vd is likely to increase $T_{1/2}$.

CL, and therefore $T_{1/2}$, can be affected by the disease process that occurs in critically ill patients and from interventions of the intensivist. Standard initial management of hypotension that critically ill patients may develop is administration of intravenous fluids. When hypotension persists, vasopressor agents are prescribed. It is, therefore, not surprising that critically ill patients often have higher than normal cardiac indices (13, 22). Some information suggests that mechanical ventilation may cause decreased antibiotic CL (19). In the absence of significant organ dysfunction, there is often an increased renal perfusion and consequently increased creatinine clearance and elimination of hydrophilic antibiotics (23–25). It follows that dose adjustment for hydrophilic antibiotics can be guided by measures of creatinine clearance even in patients with significant burn injuries (19). Strong evidence suggests that the most effective way to calculate renal function remains using an 8, 12, or 24-hour creatinine clearance collection (26, 27), although recent work has suggested that a 2-hour creatinine clearance may be an adequate substitute (28). It must be emphasized that equations such as the Cockroft-Gault (29) and Modified Diet in Renal Disease (30) equations are likely to be unreliable and, if possible, should not be substituted for urinary creatinine clearance data (31).

Further evidence suggests that critically ill patients may have higher creatinine clearances even in the presence of normal plasma creatinine concentrations (32, 33). A subsequent higher CL of renally eliminated drugs may result in a decreased $T_{1/2}$.

Hypoalbuminemia. Protein binding is a factor that may influence the Vd and CL of many antibiotics. A notable example of this pharmacokinetic alteration exists for ceftriaxone, which is 95% bound to albumin in normal ward patients (34, 35). In hypoalbuminemic states, as common in critically ill patients, this can result in a higher unbound concentration that has a 100% increased CL and 90% greater Vd (36). Other highly protein-bound antibiotics that probably develop altered pharmacokinetics from hypoalbuminaemia include oxacillin and teicoplanin.

Development of End-Organ Dysfunction. With further deterioration in the health status of the patient, significant myocardial depression can occur, which leads to a decrease in organ perfusion and failure of the microvascular circulation (37). This may then progress to multiple organ dysfunction syndrome, which may include renal and/or hepatic dysfunction (38). This will result in decreased antibiotic CL, prolonged $T_{1/2}$, and potential toxicity from elevated antibiotic concentrations and/or accumulation of metabolites. For some drugs, if dysfunction of the primary eliminating organ occurs, other organs may increase their intrinsic CL causing little change in expected plasma concentration (e.g., in renal dysfunction, ciprofloxacin transintestinal CL can increase, resulting in only a small decrease in total body CL) (39). Preliminary data also support increased biliary CL of ticarcillin and piperacillin in renal dysfunction (40, 41).

Figure 3 schematically identifies the pharmacokinetic changes that can occur because of the altered physiology in critical illness.

When renal dysfunction is present or if the patient needs renal replacement therapy, standard texts or review articles should be used as a guide for altered dosing (42–44).

Tissue Penetration. Antibiotic pharmacokinetics at the target site, which is usually tissue (45), are important to predict antibiotic-bacteria interactions. Microdialysis is an *in vivo* sampling technique that is the subject of an increasing number of research publications, particularly in critically ill patients (46–49).

The current data suggest that antibiotic penetration into tissues of patients with septic shock is impaired, possibly up to five to ten times lower than in healthy volunteers, although in other patients with sepsis but without shock there seems to be a less significant effect on tissue concentrations (47–49). Therefore, dosing of antibiotics at high doses is probably required to maximize antibiotic penetration, particularly in patients with shock, although data to support this is currently lacking.

The potential pharmacokinetic variability for many antibiotics requires the clinician to develop dosing strategies that account for altered pharmacokinetics and pathogen susceptibility studies in each patient. Such individualized dosing may facilitate optimized patient outcomes. Ongoing evaluations of sickness severity can facilitate timely adjustment of antibiotic dosing.

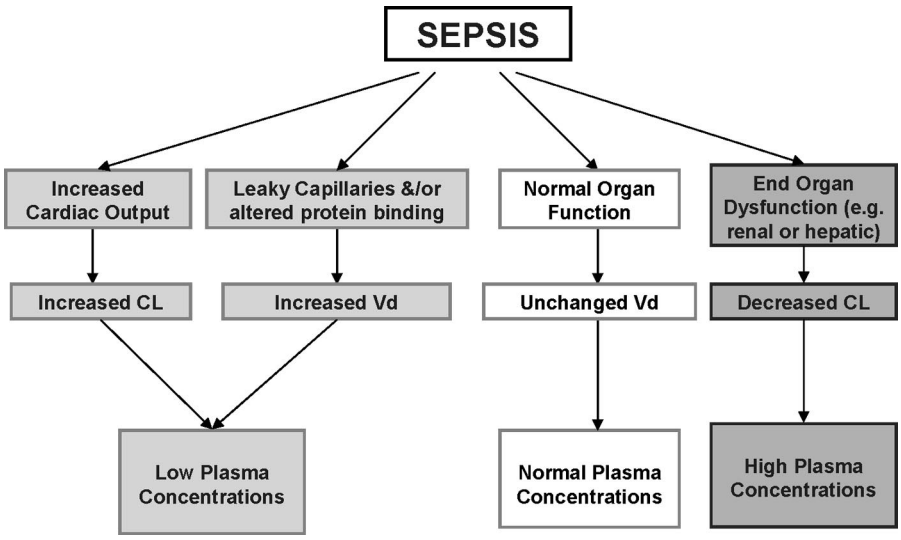

Figure 3. Schematic representation of the basic pathophysiological changes that can occur during sepsis and their subsequent pharmacokinetic effects. Note that there can be significant overlap between the groups above enabling multiple permutations for altered drug pharmacokinetics, e.g. patients with mild-to-moderate renal failure may develop increased transintestinal clearance of ciprofloxacin resulting in relatively normal plasma concentrations (39). *CL*, clearance; *Vd*, volume of distribution.

Specific Antibiotic Classes

General pharmacokinetic and pharmacodynamic characteristics will be considered for aminoglycosides, β-lactams, glycopeptides, fluoroquinolones, lincosamides as well as tigecycline, linezolid, and colistin. The clinical application and dosing implications of these properties for critically ill patients will also be addressed. Table 2 describes the potential altered pharmacokinetics of these antibiotics in critically ill patients.

Table 2. General PK characteristics of various antibiotics and possible changes that can occur during fluid shifts in critically ill patients

Antibiotic Class	Vd (L/kg)	Increased Vd with Fluid Shifts?	Decreased C_{max} with Fluid Shifts?	Plasma $T_{1/2}$ (hrs)	Protein Binding	Altered CL in Critically Ill?	TDM Required?
Aminoglycosides (61, 62, 67)	0.2–0.3 (consistent with extracellular water)	Yes	Yes	2–3	Low	Varies proportionately with renal function	Yes, to ensure high C_{max} and adequate CL
β-lactams (33, 70, 155, 156)	Variable but consistent with extracellular water	Yes	Yes	0.5–2 (except ceftriaxone 6–9 hrs)	Low (except ceftriaxone and oxacillin)	Varies proportionately with renal function (some exceptions)	No
Carbapenems (90, 91)	Variable but consistent with extracellular water	Yes	Yes	1 (except ertapenem 4 hrs)	Low (except ertapenem)	Varies proportionately with renal function	No
Glycopeptides (17, 105)	0.2–1.6 (consistent with extracellular water)	Yes	Yes	4–6 (vancomycin) 80–160 (teicoplanin)	30% to 55% (vancomycin) 90% (teicoplanin)	Varies proportionately with renal function. Increased teicoplanin CL in hypoalbuminemia	Yes, to ensure plasma C_{min} >15 mg/mL
Tigecycline (132–134)	7–10	Unlikely	Unlikely	37–66	73% to 79%	May decrease with cholestasis	No
Clindamycin (138, 140)	0.6–1.2	No	Yes	1.5–5	65% to 90%	Decreased hepatic CL	No
Linezolid (130)	0.5–0.6	Yes	Yes	3.5–7	31%	PK changes in critical illness probably not clinically significant	No
Colistin (143, 146, 147)[a]	0.18–1.5 (assuming 60 kg patient)	Likely	Likely	2–7.4	Unknown	Varies proportionately with renal function	No

Vd, volume of distribution; CL, clearance; PK, pharmacokinetic; TDM, therapeutic drug monitoring.
[a]Very little accurate pharmacokinetic data exists for colistin because of a lack of reliable analytical methods (141).

Aminoglycosides. Dosing of aminoglycoside antibiotics has been vigorously debated in the literature because of the narrow therapeutic index of these drugs. The kill characteristic of the aminoglycosides is concentration dependent (50–54), with a significant postantibiotic effect that can prevent bacterial regrowth for prolonged periods should drug concentrations fall below the minimum inhibitory concentration (MIC) (51–54). Such pharmacodynamic properties have stimulated research that has supported once daily administration as opposed to small, multiple doses (50, 55–58). It is considered that high minimum concentration (C_{min}), or more specifically the area under the concentration-time curve (AUC), are more closely correlated with the well-documented adverse renal and ototoxic effects of these hydrophilic drugs (50, 55, 56), although recent data suggest a genetic predisposition to ototoxicity (59).

Aminoglycosides often have increased Vd in critically ill patients that can result in a decreased maximum concentration (C_{max}) (60–65). This increased Vd has been shown to increase proportionally with increasing levels of sickness severity (66). Maximal weight-based dosing (e.g., tobramycin/gentamicin 7 mg/kg) consistently achieves adequate C_{max}:MIC ratios (62). In burn patients (61) and patients undergoing mechanical ventilation (65), an increased Vd has been shown to prolong $T_{1/2}$. However, creatinine clearance is likely to be more descriptive of aminoglycoside CL (67). Such pharmacokinetic variability and potential for adverse effects mandates that monitoring of plasma aminoglycoside concentrations is essential. Although Bayesian dosing methods may be used, use of dosing nomograms should be avoided as they have been invalidated in critically ill patients (62, 68). To optimize aminoglycoside:bacterial effectiveness in critically ill patients, extended-interval dosing with C_{max} monitoring and MIC determination of the pathogen remains ideal practice. However, given the apparent success of mg/kg dosing (62), a low C_{min} (preferably undetectable concentration) should be obtained to minimize aminoglycoside toxicity. Multiple doses per day should only be considered for the treatment of endocarditis or in neutropenic patients.

β-Lactam Antibiotics. The β-lactam group of antibiotics consists of penicillins, cephalosporins, and monobactams. Although these antibiotics are generally hydrophilic molecules that are renally cleared with moderate-to-low protein binding, there is variability within this group [e.g., ceftriaxone has a longer $T_{1/2}$—5.8 to 8.7 hours in adults—and high protein binding—>95% (34, 35)]. In conventional bolus dosing regimens, plasma concentrations of these antibiotics may fall to low levels between doses (33, 69, 70).

In vivo animal experiments have demonstrated that β-lactams have a slow continuous kill characteristic that is almost entirely related to T > MIC (71). Data from a recent study by McKinnon et al (72) suggest that maintaining a T > MIC of 100% is associated with significantly greater clinical cure (82% vs. 33% $p = 0.002$) and bacteriologic eradication (97% vs. 44%; $p < 0.001$) in patients with severe infections. Other studies have demonstrated maximum killing of bacteria at four to five times MIC (73, 74). As such, concentrations of β-lactam antibiotics should be maintained at four to five times the MIC for extended periods during each dosing period (51, 52, 54). This would be especially appropriate in patient groups likely to have compromised host-defenses, including critically ill patients. Research shows that an improved pharmacodynamic profile is obtained with either more frequent dosing or extended or continuous infusions (70, 73, 75–80). This mode of administration is likely to be of high value if the patient develops a high glomerular filtration rate and/or increased volume of distribution, which commonly occurs in critically ill patients receiving β-lactams (33, 70, 79, 81–83). Some data exist to suggest that some β-lactams, such as piperacillin and ticarcillin, are likely to have increased biliary CL in the absence of renal CL (40, 41). The clinical implications of this situation are likely to be significant when a patient develops moderate renal and hepatic dysfunction leading to greatly reduced antibiotic CL (84–86). Seizures have been noted with high β-lactam exposures but are relatively uncommon.

Support for reduced mortality from extended infusions (4-hour infusion every 8 hours) of piperacillin-tazobactam was described in a recent cohort study of 194 seriously ill patients with *Pseudomonas aeruginosa* infection by Lodise et al (87). In this study, patients receiving extended infusions with an Acute Physiology and Chronic Health Evaluation II score ≥17 had a significantly lower 14-day mortality rate (12.2% vs. 31.6%; $p = 0.04$) than those receiving bolus infusions. Data on clinical cure superiority of continuous infusions of β-lactam antibiotics also exist. In a retrospective cohort study in patients with ventilator-associated pneumonia, Lorente et al (88) described superior clinical cure when given a continuous infusion (90.5%) compared with extended infusion (over 30 minutes; 59.6%). Roberts et al (89) described advantages for clinical cure in patients receiving ceftriaxone by continuous infusion when 4 or more days of therapy was required. No difference was found in the intention-to-treat analysis of this article, though. Further research is required to quantify the clinical utility of administering β-lactams as a continuous infusion.

Carbapenems. Carbapenems have very similar pharmacokinetic properties to β-lactams (Table 2). Pharmacodynamically, they are time-dependent antibiotics that have been reported to have maximal bactericidal activity when T > MIC is maintained for a minimum of 40% of the dosing interval. In critical illness, carbapenems are likely to develop increased Vd and higher CL (90, 91). Continuous infusion of these antibiotics has been studied, as has administration by extended infusion, which is thought to be appropriate given the low %T > MIC to optimize activity. Pharmacodynamic advantages to this method of dosing have been well described (92–94) and appear highly appropriate for use in critically ill patients.

Glycopeptides. Glycopeptides are relatively hydrophilic antibiotics that include vancomycin and teicoplanin. The optimal pharmacodynamic properties of glycopeptides have not been completely elucidated. Some *in vitro* and animal data suggest that the bactericidal activity of vancomycin is time dependent (95–97), whereas other data from a nonneutropenic mouse model found C_{max}:MIC to correlate with efficacy (98). Other studies have proposed that AUC:MIC is the pharmacokinetic and pharmacodynamic parameter correlated with efficacy (10, 99).

As such there is little consensus on whether C_{max}:MIC or T > MIC should be maximized in dosing regimens. Previous studies examining continuous infusion of vancomycin have not provided conclusive results. Wysocki et al (100) found no clinical advantages for continuous infusion of vancomycin compared with intermittent dosing in 160 patients. However, recently Rello et al (101), described a suggestion of clinical superiority for continuous infusion of vancomycin in a subset of pa-

Table 3. General PK characteristics of fluoroquinolone antibiotics and possible changes that can occur during fluid shifts in critically ill patients

Fluoroquinolone	Vd (L/kg)	Increased Vd with Fluid Shifts?	Decreased C_{max} with Fluid Shifts?	Plasma $T_{1/2}$ (hrs)	Protein Binding	Altered CL with Renal Dysfunction?	Normal Dose	Dose Adjustment in Renal Dysfunction?
Ciprofloxacin (157–159)	1.2–2.7	No	Yes	3 (4–5 hrs in the elderly)	20% to 40%	No	IV 400 mg 8 hourly	Yes
Levofloxacin (109–111)	0.92–1.36	No	Yes	6–8.9	24% to 38%	Yes	500–750 mg daily (May increase to 1000 mg daily in critically ill patients with sepsis	a) CrCL = 20–49 mL/min → 250–500 mg daily; b) CrCL is 10–19 mL/min → 250–500 mg 48-hourly
Moxifloxacin (160–162)	2.45–3.55	No	Yes	9.3–15.6	39% to 52%	No	400 mg daily	No
Gatifloxacin (163, 164)	1.98–2.31	No	Yes	6.5–9.6	20%	Yes	400 mg daily	CrCL ≤40 mL/min → 400 mg initial dose followed by 200 mg 24-hourly

PK, pharmacokinetic; CL, clearance; CrCL, creatinine CL; C_{max}, maximum concentration; IV, intravenous.

tients treated for ventilator-associated pneumonia caused by methicillin-resistant *Staphylococcus aureus*.

Like most β-lactams, glycopeptide CL is closely related to creatinine clearance. Nonrenal CL of vancomycin has been well described and shown to increase in patients with acute renal failure, although it displays significant variability among patients (102). In obese patients, weight-based dosing (~30 mg/kg) that uses total body weight appears appropriate although such patients may require more frequent dosing (103). Therefore, empirical dosing based on creatinine clearance data with subsequent therapeutic drug monitoring of C_{min} plasma concentrations (suggested C_{min} 15–20 mg/L) is recommended (104–106). It should be noted that recent data report higher rates of nephrotoxicity with high vancomycin dosing when higher C_{min} concentrations (≥15 mg/L) are present (107). Nephrotoxicity will be potentiated by coadministration with other nephrotoxic drugs such as aminoglycosides or amphotericin.

Fluoroquinolones. Fluoroquinolones are lipophilic antibiotics that include ciprofloxacin, moxifloxacin, levofloxacin, and gatifloxacin. All fluoroquinolones have extensive distribution characteristics and achieve good extracellular and intracellular concentrations with excellent penetration of neutrophils and lymphocytes (108). The Vd of most fluoroquinolones is minimally affected in the critically ill patient, although levofloxacin requires increased dosing in critically ill patients because of a decreased $T_{1/2}$ (resulting in an AUC reduced by 30% to 40%) (109–111). The pharmacokinetics of selected fluoroquinolones are described in Table 3.

Fluoroquinolones not only display largely concentration-dependent kill characteristics, but also some time-dependent effects. Previous research has suggested that achieving a C_{max}:MIC ratio of 10 for ciprofloxacin is the critical variable in predicting bacterial eradication (112–114). Forrest et al studied ciprofloxacin in critically ill patients and concluded that achieving an AUC:MIC greater than 125 is associated with a successful clinical outcome (115). This result is necessary for Gram-negative organisms with Gram-positive organisms requiring an AUC:MIC of 30 (115–118). Inappropriate low dosing of ciprofloxacin has also been associated with the emergence of resistant bacterial strains (particularly enterococci, pseudomonas and methicillin-resistant *Staphylococcus aureus*) (9, 119–121). For Gram-negative bacteria, this may occur when AUC:MIC <100 (122, 123). Therefore, AUC:MIC and C_{max}:MIC are pharmacodynamic variables that require close attention for optimal fluoroquinolone usage. Dosing should seek to maximize C_{max}:MIC as this will drive adequate AUC:MIC exposures. The principal adverse effects that may occur with drug toxicity include QT-interval prolongation as well as confusion and dizziness. The latter two effects may affect any cognition evaluations by the healthcare staff of critically ill patients.

Linezolid. Linezolid belongs to a new class of antimicrobials called the *oxazolidinone*. Although linezolid is quite hydrophilic, it distributes widely into tissues and is mostly metabolized hepatically before being cleared renally (124, 125). At this time, no dose adjustment is recommended in renal dysfunction or hepatic dysfunction (125, 126). From a pharmacodynamic perspective, maintaining a T > MIC of 40% to 80% is thought to be the major predictor of efficacy (10, 127–129). A 600-mg 12-hourly dose should achieve this ratio in humans against susceptible organisms with MICs up to 2–4 mg/L. Linezolid $T_{1/2}$ has been shown to be shorter and Vd is larger in critically ill patients, although these are probably not significant (130).

A significant area of interest for the intensivist should be the potential for adverse effects associated with linezolid and drug interaction with other agents that may inhibit monoamine oxidase (125). Although linezolid is generally safe and well tolerated for up to 28 days at 600 mg twice daily (131), evidence exists that therapy longer than 14 days can cause reversible myelosuppression (132). As such, as part of individualized patient-specific therapy, patients prescribed linezolid may require complete blood counts ordered [up to weekly (131)] to monitor for hematologic adverse effects.

Tigecycline. Tigecycline is a member of the glycylcyclines that are novel tetracyclines with Gram-positive and Gram-

negative activity. Pharmacokinetically, tigecycline possesses lipophilic characteristics that enable rapid and extensive penetration into body tissues (133). It is primarily eliminated by biliary excretion with only 15% of the dose eliminated unchanged in urine (134). There are few data to support potentially altered pharmacokinetics in critically ill patients. Pharmacodynamically, although tigecycline displays time-dependent killing against some bacteria (135), AUC:MIC is more likely to be correlated with efficacy (132, 133). This is because of its long $T_{1/2}$ and prolonged postantibiotic effect.

Lincosamides. The lincosamide antibiotics include clindamycin and lincomycin. This lipophilic class of antibiotics achieves wide distribution throughout the body and achieves therapeutic concentrations in most body compartments (136–138). T > MIC has been determined to be the pharmacodynamic factor correlated with efficacy. Free drug levels of lincosamides should exceed the MIC of the infective pathogen for at least 40% to 50% of the dosing interval (139). Hepatic CL of clindamycin is documented to decrease in critically ill patients with sepsis (140). Antibiotic-associated diarrhea is a significant adverse effect for this class of antibiotics.

Colistin. The polymyxin antibiotics (e.g., colistin) were first used in the 1960s and subsequently lost appeal because of associated nephro- and neurotoxicities (141). With the escalation of antibiotic multi-drug resistance, it is now being increasingly used as an alternate antibiotic. Colistin is administered typically as colistimethate sodium (sodium colistin methanesulphate). This molecule is hydrolyzed to sulfomethylated derivatives and colistin (142). It is a hydrophilic molecule for which little pharmacokinetic information exists (143). Pharmacodynamically, it is thought to have predominantly concentration-dependent bacterial killing activity (141, 144, 145).

Colistin is available as two formulations Colomycin Injection (40, 80, and 160 mg colistimethate per vial) and Coly-Mycin Parenteral (400 mg colistimethate per vial, Forest Laboratories, Bexley, UK), which contain differing amounts of colistimethate sodium per vial; ERFA, Montreal, Canada. Patient dosing should follow weight and renal dysfunction considerations where possible (146). Comparative data between critically ill patients and other patients is currently lacking and dosing remains a difficult issue with little consensus on appropriate dosing strategies existing (143, 146, 147).

General Dosing Considerations. The importance of effective antibiotic therapy in the ICU mandates intensivists to select effective dosing regimens for critically ill patients. Table 4 proposes some general dosing recommendations that could be considered to this end. However, because of the large spectrum of different ICU admission diagnoses and the effect of the

Table 4. Broad guidelines that can be used to assist antibiotic dosing adjustment for critically ill patients

	Suggested Dosing Adjustment for Critically Ill Patients	
Antibiotic Class	Normal Renal Function	Moderate to Severe Renal Dysfunction Comments
Aminoglycosides	Use high doses (e.g., gentamicin 7 mg/kg) where possible to target C_{max}:MIC ratio of 10; monitor C_{min} and aim for undetectable plasma concentrations[a]	Use high doses where possible and monitor C_{min} thereafter (36 to 48 hourly extended interval dosing acceptable); dosing can be guided by MIC data if available if dose reductions are essential
β-lactams Carbapenems	Consider extended or continuous infusion or more frequent dosing to ensure T > MIC; therapeutic drug monitoring may be useful if available	If intermitted dosing used, dosing can occur at reduced dose or frequency (not both); err toward larger doses as β-lactams have large therapeutic window
Glycopeptides	Dosing at 30–40 mg/kg/day (vancomycin), which can be increased according to C_{min} plasma concentrations (aim for 15–20 mg/L); continuous infusions should be used when difficulty obtaining therapeutic C_{min}	High dosing on day 1 may be required to ensure adequate distribution; dose adjustments should occur according to C_{min} concentrations
Fluoroquinolones	Doses that achieve high C_{max}:MIC ratio should be targeted (e.g. ciprofloxacin 1200 mg/day); levofloxacin may require 500 mg 12-hourly in some patients with high creatinine clearance; where high doses used, monitor for toxicity (seizures)	Dose adjustment is probably only required in renal impairment for levofloxacin, gatifloxacin, and ciprofloxacin; where possible reduce frequency and maintain dose
Tigecycline	Use 100 mg loading dose then 50 mg 12 hourly	No dose adjustment required in renal failure or dialysis[b]
Linezolid	Use 600 mg 12 hourly	No dosage adjustment required in renal failure or dialysis
Lincosamides	Use 600–900 mg 8 hourly	Decreased lincomycin dose or frequency in renal or hepatic dysfunction; decrease clindamycin dose or frequency in hepatic dysfunction
Colistin	Use 5 mg/kg/day of colistin base (75,000 international units/kg/day colistimethate sodium)[c] intravenously in 3 divided doses	Reduce dose or frequency (not both)

MIC, minimum inhibitory concentration; C_{max}, maximum concentration; C_{min}, minimum concentration.

[a]Aminoglycoside levels should be undetectable for no more than the post-antibiotic effect. We recommend a maximum of 4 hrs before redosing as any longer delay may enable bacterial regrowth; [b]if severe cholestasis present then tigecycline should be dosed with 50-mg loading dose, then 25 mg 12 hourly; [c]1 mg colistimethate sodium is equivalent to 12,500 international units (165).

different levels of organ function and pathophysiological changes that may be observed in these patients, it is not possible to provide specific dosing recommendations for each potential patient. Standard considerations of potential for adverse effects and drug interactions should always be considered as part of the antibiotic-prescribing process and any ongoing monitoring performed by the clinician or associated healthcare staff.

Appropriate Dosing May Reduce Development of Antibiotic Resistance. Antibiotic resistance continues to escalate worldwide with the ICU being a particular focus on further development. There is now sufficient data to suggest that inappropriately low antibiotic dosing may be contributing to the increasing rate of antibiotic resistance (9, 123, 148–154). Developing dosing regimens that adhere to pharmacodynamic principles and maximize antibiotic exposure appears to be essential to reduce the development of antibiotic resistance. This is probably best achieved by administering the highest recommended dose to the patient.

CONCLUSION

In summary, the solubility characteristics of antibiotics can help determine where dose adjustment may be necessary for individual critically ill patients. Hydrophilic concentration-dependent antibiotics may possess a higher Vd in critically ill patients leading to a reduced C_{max}. It follows that hydrophilic time-dependent antibiotics may develop a low C_{min} that may reduce antibiotic efficacy. Common increases in Vd need to be contrasted against potential increased or reduced antibiotic CL that can occur in these patients. Antibiotic underdosing can occur, which may in turn lead to the development of antibiotic resistance and/or therapeutic failure, if appropriate dosing adjustments are not made. For renally cleared compounds, dose prescription based on measured creatinine clearance should enable appropriate initial dosing in critically ill patients. Where possible thereafter, therapeutic drug monitoring should be considered to ensure target plasma concentrations are being achieved.

Given that most antibiotic regimens have been derived from trials with patients who are not critically ill, the intensivist must adapt his/her dosing to account for the potential altered pathophysiology of this patient group. To optimize dosing, the antibiotic's pharmacodynamic properties, as well as the potential altered antibiotic pharmacokinetics, need to be considered by the clinician. Such a process will enable dose selection that is more appropriate for use in the individual patient.

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