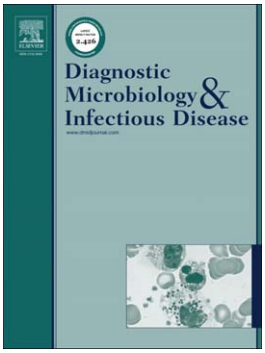
Accepted Manuscript



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PII: S0732-8893(14)00167-9
DOI: doi: 10.1016/j.diagmicrobio.2014.04.007
Reference: DMB 13602

To appear in: *Diagnostic Microbiology and Infectious Disease*

Received date: 9 April 2013
Revised date: 14 April 2014
Accepted date: 22 April 2014

Please cite this article as: Felton TW, Hope WW, Roberts JA, How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it?, *Diagnostic Microbiology and Infectious Disease* (2014), doi: 10.1016/j.diagmicrobio.2014.04.007

How severe is antibiotic pharmacokinetic variability in critically ill patients and what can be done about it?

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Dr Felton is a MRC Clinical Training Fellow supported by the North West England Medical Research Council Fellowship Scheme in Clinical Pharmacology and Therapeutics, which is funded by the Medical Research Council (grant number G1000417/94909), ICON, GlaxoSmithKline, AstraZeneca and the Medical Evaluation Unit. Professor Hope is supported by a Clinician Scientist Fellowship from the National Institute of Health Research. Dr Roberts is funded by a Career Development Fellowship from the National Health and Medical Research Council of Australia (APP1048652).

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Abstract

The pharmacokinetics of antimicrobial agents administered to critically ill patients exhibit marked variability. This variability results from pathophysiological changes that occur in critically ill patients. Changes in volume of distribution, clearance and tissue penetration all affect the drug concentrations at the site of infection. Pharmacokinetic-pharmacodynamic indices (fC_{max}:MIC; AUC_{0-24}:MIC; $fT_{>MIC}$; fC_{min}:MIC) for both antimicrobial effect and suppression of emergence of resistance are described for many antimicrobial drugs. Changing the regimen by which antimicrobial drugs are delivered can help overcome the pharmacokinetic variability and optimize target attainment. This will deliver optimised antimicrobial chemotherapy to individual critically ill patients. Delivery of β-lactams antimicrobial agents by infusions, rather than bolus dosing, is effective at increasing the duration of the dosing interval that the drug concentration is above the MIC. Therapeutic drug monitoring, utilising population pharmacokinetic mathematical models with Bayesian estimation, can also be used to optimise regimens following measurement of plasma drug concentrations. Clinical trials are required to establish if patient outcomes can be improved by implementing these techniques.

Introduction

Extreme pharmacokinetic (PK) variability of antimicrobial agents is encountered in critically ill patients often as a result of alterations in cardiac output, tissue perfusion, end-organ dysfunction, capillary leakage and hypoalbuminaemia (Boucher et al. 2006). The resultant variability in drug exposure combined with the frequent presence of resistant micro-organisms may lead to suboptimal clinical outcomes. Sepsis affects one-third of patients on the intensive care unit (ICU) and is associated with a high mortality rate (Martin et al. 2003; Vincent et al. 2006). At any given time, approximately two-thirds of patients in the ICU are receiving antimicrobial agents. Mounting evidence suggests that currently marketed antimicrobial dosing regimens may not necessarily be optimal for these patients (Kollef 1999; Roberts and Lipman 2006; Vincent et al. 2009). Significant changes in the clinical PK of antimicrobial agents are common in critically ill patients and dosing that does not account for these may be associated with a higher likelihood of treatment failure (Ambrose et al. 2010).

For antimicrobials agents, pharmacodynamics (PD) is the discipline that links drug exposure (e.g. drug concentrations) with bacterial killing or the inhibition of bacterial growth. Clinically relevant endpoints for PD studies include the antimicrobial effect, the emergence of drug resistance and antimicrobial drug toxicity. PD relationships can be established in pre-clinical and clinical contexts and both provide an insight into the magnitude of the antimicrobial drug exposure that is required for optimal effect.

The objective of this paper is to describe the antimicrobial PK variability present in critically ill patients and then to outline how PK and PD principles can be applied to deliver optimal dosing strategies.

Why is pharmacokinetics important in critically ill patients?

Pharmacokinetics describes the time-course of drug concentrations in the body. PK parameters can explain why a drug may display a different concentration-time profile in one patient

group versus another. The apparent volume of distribution (Vd) of the drug, the clearance (Cl) and tissue distribution are all essential data for defining whether an antimicrobial dose will result in effective concentrations at the site of infection.

Volume of distribution. The Vd is a proportionality constant that relates the amount of drug in the body to the observed concentration in serum/plasma. An increase in Vd results in a reduction in peak drug concentration, an increase in trough drug concentration while the area under the concentration time curve remains unchanged. Changes in the Vd of antimicrobials in critically ill patients results from critical illness-related pathophysiology and consequent medical interventions such as fluid resuscitation. The effect on changes to Vd is predominantly restricted to hydrophilic drugs, such as β-lactams, aminoglycosides, glycopeptides, linezolid and colistin (Tang et al. 1999; Lipman et al. 2001; Boselli et al. 2005; del Mar Fernández de Gatta Garcia et al. 2007; Roberts et al. 2009a; Taccone et al. 2010; Sime et al. 2012). These compounds typically exhibit a low Vd that often increases in critically ill patients which causes standard doses to have lower concentrations than in a non critically ill patient (Roberts and Lipman 2009). Increasing extra-vascular water or severity of critical illness is associated with an increase in the Vd for hydrophilic agents such as aminoglycosides (Triginer et al. 1990; Marik 1993; Lugo and Castañeda-Hernández 1997; Balik et al. 2005). Hypoalbuminaemia increases the Vd of both aminoglycosides and flucloxacillin (Lugo and Castañeda-Hernández 1997; Ulldemolins et al. 2010). The Vd for lipophilic drugs, such as fluoroquinolones, is usually high, but often unchanged in critical ill patients compared to healthy volunteers (Roberts and Lipman 2009). Extra-corporeal circuits, such as extra-corporeal membrane oxygenation and renal replacement therapy, alter the Vd of some antimicrobial agents, although this may be due to drug adsorption to circuit materials. Binding of antimicrobial agents to extra-corporeal circuits is not consistent between drug classes. Reduced plasma antimicrobial concentrations have been shown with gentamicin and voriconazole, which have been shown to avidly bind to some circuits, while plasma concentrations of other antimicrobial agents, such as caspofungin, are unaffected by the

presence of an extra-corporeal circuit (Dodge et al. 1994; Mulla et al. 2000; Mehta et al. 2007; Spriet et al. 2009).

Clearance. The Cl of a drug is defined as the volume of plasma completely cleared of drug per unit time. Clearance of antimicrobial agents may be due to metabolism and/or excretion. Renal excretion of antimicrobials agents is particularly affected during critical illness.

Clearance of β-lactams, fluoroquinolones, aminoglycosides, vancomycin and linezolid is altered in critically ill patients and primarily relates to changes in function of the eliminating organ (e.g. kidneys, liver, biliary tract) (Triginer et al. 1990; Tang et al. 1999; Boselli et al. 2005; del Mar Fernández de Gatta Garcia et al. 2007; Fish 2007; Roberts et al. 2009a; Taccone et al. 2010). A reduction in glomerular filtration rate, as occurs in acute kidney injury, reduces the Cl of renally cleared antibiotics (Isla et al. 2008; Georges et al. 2009; Nicasio et al. 2009; Revilla et al. 2010; Crandon et al. 2011). In contrast, augmented renal clearance may occur with some antimicrobials as a result of increased renal perfusion caused due to high cardiac output and low systemic vascular resistance associated with sepsis. In these cases Cl of some antimicrobials may even triple (Ambrose et al. 2010; Udy et al. 2011). Enhanced Cl may occur with highly protein bound antimicrobial agents, such as flucloxacillin and ceftriaxone, as a result of hypoalbuminaemia (Burkhardt et al. 2007; Ulldemolins et al. 2010). Renal replacement therapy is an effective Cl mechanism for antimicrobial agents but marked variability in performance of Cl by renal replacement therapy has been described (Tegeder et al. 1999; Krueger et al. 2003; Lipman et al. 2003; Arzuaga et al. 2005; Dagenais and Keller 2009; Bilgrami et al. 2010). Hepatic dysfunction in critically ill patients also affects elimination of drugs, such as ciprofloxacin, moxifloxacin and ceftriaxone, which are metabolised by the liver or undergo transintestinal Cl (Heinemeyer et al. 1990; Jones et al. 1997; Stass et al. 2002).

Target site penetration of drugs. The plasma drug concentration is the easiest and most frequently measured PK observation. For antimicrobials agents, infection mostly occurs in the

interstitial fluid (ISF) of tissues meaning that the plasma concentration is in fact a substitute for antimicrobial concentrations at the site of infection (Ryan 1993; Felton et al. 2014). Therefore, plasma concentrations provide a reliable surrogate marker in patient groups and drugs where equivalent concentrations between plasma and tissue can be expected (Drusano 2004). However, tissue penetration studies using microdialysis catheters suggest impaired tissue penetration with some antimicrobial agents in critically ill patients (Joukhadar et al. 2001; Roberts et al. 2009a, 2009b). Low ISF concentrations, as much as one-tenth the observed in plasma have been described and it has been postulated that higher than normal plasma concentrations should be targeted to drive antimicrobial drugs into tissue as a means of increasing ISF concentrations (Joukhadar et al. 2001; Roberts et al. 2009a, 2009b). Other studies describing penetration of antimicrobial agents into the epithelial lining fluid (ELF) of the lung from plasma show aminoglycosides, β-lactams and glycopeptides will generate a ratio of ELF to unbound plasma free-drug concentrations of ≤ 1 (Drusano et al. 2011; Lodise et al. 2011). The ratio of ELF to plasma concentrations of linezolid, macrolides and fluoroquinolones is typically greater than one (Rodvold et al. 2011). The clinical consequences of impaired penetration is yet to be defined, but may in part explain the findings of some clinical evaluations that have proposed that plasma antimicrobial agent concentrations, higher than previously considered necessary, may be required for clinical cure in some critically ill patients (Tam et al. 2002).

Why is pharmacodynamics important in critically ill patients?

PK-PD indices. Three measures of drug exposure are commonly used to link drug exposure with bacterial killing (Craig 1998; Drusano 2004; Ambrose et al. 2007). Firstly, the fraction of the dosing interval that the concentration of unbound (free) drug is greater than MIC ($fT_{>MIC}$); secondly, the ratio of the area under the unbound drug concentration (fAUC) time curve to the MIC (fAUC/MIC) and finally the ratio of the peak unbound drug concentration during a dosing interval to the MIC (fCmax/MIC). Table 1 describes the PK-PD indices for selected antimicrobial agents.

Toxicity. Concentration or exposure-dependent antimicrobial agent-related toxicities have been described for many antimicrobial classes. The probability of nephrotoxicty related to administration of gentamicin is related to the area-under-the-concentration time curve (Rybak et al. 1999). Concurrent administration of vancomycin results in a left-shift of the curve with an increased risk of nephrotoxicity related to lower gentamicin exposures. The risk of creatine phosphokinase elevation has been related to daptomycin trough concentration in patients with bacteremia or endocarditis (Bhavnani et al. 2010). Trough voriconazole concentrations have been shown to correlate with the probability of neurotoxicity (Pascual et al. 2008). In the context of profound PK variability in critically ill patients, many patients may be at risk of toxicities if dose adjustment is not used when reduced antimicrobial Cl is present.

Target concentrations in critically ill patients. Potential PK-PD targets,for all classes of antimicrobial agents, which may be used for therapeutic drug monitoring in critically ill patients remain poorly defined with a wide range of potential target concentrations (Table 1) (Roberts et al. 2010a).

Combining PK-PD concepts in critically ill patients.

PK variability reduces the likelihood of an acceptable proportion of patients achieving the desired PK-PD targets (Tam et al. 2003; Brink et al. 2009; Blondiaux et al. 2010; Roberts et al. 2010c; Taccone et al. 2010; Ulldemolins et al. 2011; Zelenitsky et al. 2011). Combining knowledge of each agent's specific PK and target concentrations, in critically ill patients, allows dosing regimens be altered so effective antimicrobial agents concentrations can be delivered whilst minimising the risk of toxicity (Drusano et al. 2007; Ambrose et al. 2010).

Using PK-PD concepts to optimise dosing in critically ill patients

The current practice of delivering fixed regimens of antimicrobial drugs by bolus administration or short infusion (15-60 minutes) appears sub-optimal for treating some critically ill patients. Administration of β-lactam antibiotics by extended or continuous infusion has been studied in a number of clinical trials and is being incorporated into routine clinical practice by some centres (Lodise et al. 2007; Dulhunty et al. 2012). Therapeutic drug monitoring (TDM) is routinely used for some antimicrobial drugs, such as aminoglycosides, but is primarily aimed at avoiding toxicity rather than optimising the antimicrobial effect (Roberts et al. 2010a). A variety of approaches have been developed that enable dosage adjustments based on assessment of individual patients PK-PD.

Administration of β-lactams via extended infusions. The majority of β-lactam antibiotics have relatively short half lives. Delivering β-lactam antibiotics by either prolonged infusion (an infusion lasting 40-50% of the dosing interval) or continuous infusion, reduces the peak concentration but sustains a higher concentration for a greater proportion of the dosing interval. Administration by extended infusion results in approximately the same area-under-the-concentration time curve as administration by bolus dosing or short infusion. This will increase the fraction of the dosing interval the drug concentration is above the MIC (Lodise et al. 2007).

There is only relatively limited pre-clinical in vivo data to support the use of extended infusions for administering β-lactam antibiotics. Ceftazidime delivered by infusion is superior to bolus administration especially in leukopenic rats (Roosendaal et al. 1985, 1986, 1989). In vitro data also supports the use of infusions particularly against organisms with reduced susceptibility (Mouton and den Hollander 1994; Alou et al. 2005). The most compelling support for the use of prolonged or continuous infusions comes from the results of Monte Carlo simulation (Roberts et al. 2011). Results of simulation consistently shows that delivering β-lactam antibiotics by infusion results in a greater number of subjects achieving the PK-PD target, particularly in the presence of the PK variability

common to critically ill patients (Drusano 2003; Lodise et al. 2004; Roberts et al. 2009a, 2010b; Felton et al. 2012; Roberts and Lipman 2013).

Based on the in vitro and in silico data, a number of clinical trials have compared the clinical outcomes of administration of β-lactam antibiotics by short versus extended infusion. In a recent randomised controlled trial, a significantly higher clinical cure rate was observed following administration of β-lactam antibiotics by infusion (Dulhunty et al. 2012). This landmark study is in contrast to the results of most previous trials examining the effect of infusion duration in various patient populations. The results of recent meta-analyses are also conflicting (Roberts et al. 2009c; Tamma et al. 2011; Falagas et al. 2013). The most recent meta-analysis concludes that administration of piperacillin-tazobactam or carbapenems by infusion, rather than bolus administration, is associated with a lower mortality (Falagas et al. 2013). Previous meta-analyses have shown no advantage to using infusions rather than bolus administration in hospitalised patients (Roberts et al. 2009c; Tamma et al. 2011). Falagas *et al* excluded patients administered cephalosporins which were included in the other meta-analyses. Many of the trials included in these analyses were retrospective in design or of limited power due to a small sample size. Improved outcomes related to administration of β-lactam antibiotics by infusion, rather than bolus dosing, has been shown in only the most critically unwell patients (Lodise et al. 2007). The severity of illness of patients in trials included in each of the meta-analyses may influence outcome of the analysis. Further clinical trials are required to investigate the use of extended or continuous infusions of β-lactam antibiotics.

A potential explanation for the discrepancy between the in vitro, in vivo and in silico findings and the rather disappointing clinical trial results is apparent in the simulation in Figure 1. For a low target concentration (e.g. 1 mg/L), both bolus and infusional administration produce a plasma free drug concentration above this level for most of the dosing interval. The advantage of the infusion is much more pronounced for higher target concentration (e.g. 8 mg/L). Here delivery by infusion dosing produces plasma free drug concentrations above the target for a significantly higher fraction

of the dosing interval. From the example in Figure 1, the time the free drug concentration is above 8 mg/L is 59% following bolus dosing and 100% with continuous infusion. In accordance with this, Monte Carlo simulations consistently show that the difference in target attainment between bolus administration and infusion is most pronounced when the MIC is raised.

Therapeutic drug monitoring. Historically, TDM has been used for agents exhibiting a narrow therapeutic range with potential for drug toxicity, lack of clinical parameters to adjust the dose, well-defined exposure-response relationship and unpredictable PK (International Association of Therapeutic Drug Monitoring and Clinical Toxicology 2011). In critically ill patients, many antimicrobials can exhibit highly variable PK with a therapeutic range narrowed by increasing MICs associated with antimicrobial resistance. Traditionally, modification of dosage regimens has been reserved for agents such as aminoglycosides, glycopeptides and the triazole antifungals for the purposes of reducing toxicity. With PK variability causing an increased likelihood of sub-therapeutic antimicrobial concentrations, TDM may also be useful to ensure that patients achieve PK-PD targets.

TDM requires an understanding of the PK and PD relationship integrated with the clinical features of the patient. TDM may be divided into two types: *a priori* and *a posteriori* (International Association of Therapeutic Drug Monitoring and Clinical Toxicology 2011). In *a priori* TDM the starting dosage regimen is altered based on knowledge of a patient and the organism. The use of weight-based loading doses of aminoglycosides or glycopeptides antimicrobial agents in critically ill patients is an example. In contrast, in *a posteriori* TDM, knowledge of patient, likely pathogen MIC and a target range for plasma drug concentrations is typically required. Dosage regimen alteration may then be guided by measured drug concentrations. This form of TDM may involve dosing algorithms or computerised Bayesian predictions (Lesko and Schmidt 2012).

Relatively few studies have assessed the impact of TDM in critically ill patients (Sime et al. 2012). The most compelling evidence is for aminoglycosides where TDM has been shown to reduce toxicity and length of hospital stay, and mortality in patients with Gram negative infections (van

Lent-Evers et al. 1999; Drusano and Louie 2011). Other studies utilising TDM include β-lactams, vancomycin, teicoplanin and linezolid (Pea et al. 2003, 2006, 2010; Darley and MacGowan 2004; Rybak et al. 2009; Scaglione et al. 2009; Delattre et al. 2010; Roberts et al. 2010c; Udy et al. 2010).

In Bayesian dose adaptation, the dose of the drug is adjusted to optimise the individual patient's exposure. Information about the specific patient, in the form of plasma drug concentrations, and a population PK model, from a relevant population, are utilised to determine the actual PK in the subject. This data can then be used to develop more specific dosing regimens individualised to the subject's needs. As the number of blood sample measurements of a new subject increases, the estimates of the PK parameters become less informed by the population and more by the individual which increases the accuracy of subsequent predictions.

An example of Bayesian dosing in practice. A critically ill patient could be given the first dose of a chosen antimicrobial at the standard dosage. During the first dosage interval, 2-3 blood samples could then be taken, at maximally informative PK sampling times, to estimate the PK of the antimicrobial. The PK samples would then be assayed in the clinic and the drug concentrations inputted into a dose optimisation software package capable of performing MAP Bayesian estimation. The dosage could then be adjusted to deliver the next dose with a PK exposure that is optimal for the individual patient.

There are a number of software packages which may be used for dosage adaption (Fuchs et al. 2013). Optimised dosing using an estimation of an individual's PK to identify the optimal dosage has not been undertaken with anti-bacterial agent. Pilot studies, within other infectious diseases areas, have demonstrated with HIV drugs in paediatric patients and in the management of invasive pulmonary aspergillosis with voriconazole (Neely and Jelliffe 2010; Hope et al. 2013). The impact of dosage adaptation on patient outcome requires further study.

Summary

Infection remains a significant problem in critically ill patients. Mortality from sepsis has not reduced in the last twenty years. The emergence of multi-drug resistant pathogens and the limited supply of new antimicrobial agents make treatment of infection in critically ill patients an even more concerning healthcare issue. The pathophysiological changes of critical illness result in marked PK variability between patients. This variability can lead to under-dosing (treatment failure) or over-dosing which may be associated with drug toxicity. Limited information is available on the optimal drug concentrations and exposures required to treat infections in critically ill patients.

Individualising antimicrobial dosing regimens offers a potentially useful approach for optimising treatment in critically ill patients. Delivery of β-lactam antibiotics by extended infusion changes the drug concentration-time profile to increase the fraction of the dosing interval the drug concentration is above the MIC. Extended infusions are likely show their largest advantage compared with bolus dosing or short infusions against organisms with an MIC approaching the breakpoint. Alternatively, dosage adaptation following TDM can, and should be used to deliver the optimal regimen to individual patients. Practical issues related to sample collection, rapid point-of-care drug assays plus access and knowledge of dose optimisation software would need to be overcome before dose optimisation could be implemented into clinical care. Further studies are needed to identify regimens which maximise antimicrobial activity and reduce the emergence of antimicrobial resistance. Regimens may include dosages of antimicrobial agents which are higher than current dosages and combinations of antimicrobial drugs. New clinical trials are required to investigate the impact of TDM on the safety and efficacy of existing antimicrobial agents.

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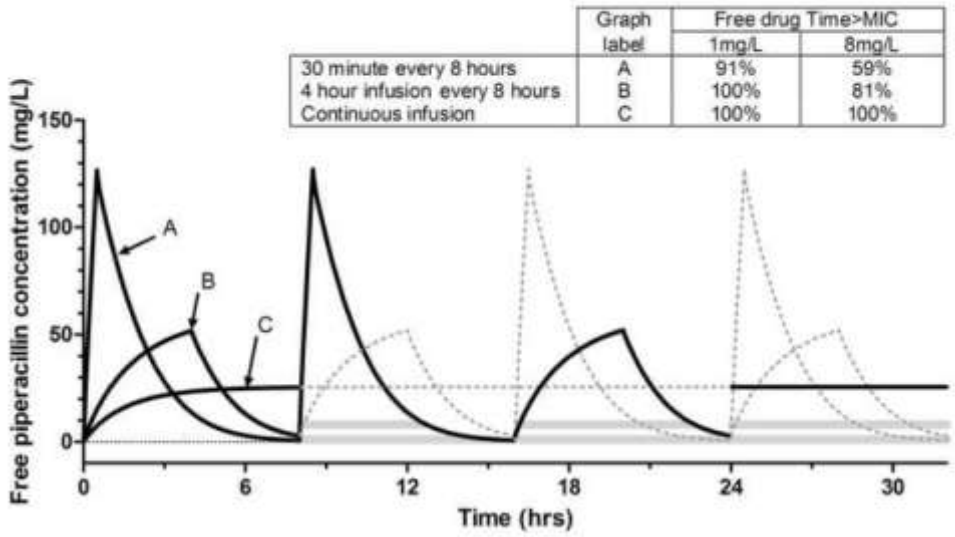
Figures.

Figure 1. Figure illustrating the concentration-time profile of unbound piperacillin following administration of piperacillin 4 grams over 30 minutes, 4 hours or by continuous infusion every 8 hours. The solid grey areas illustrate the fraction of the dosing interval that the free drug concentration is above 1 and 8mg/L. [Figures is generated by simulation, of 4g piperacillin administered over 30 minutes every 8 hours, over 4 hours every 8 hours and as a continuous infusion, in Adapt 5 (D'Argenio et al. 2009) using the median parameter estimates for piperacillin (Felton et al. 2012).]



Tables

Table 1. Proposed optimal PK-PD indices and associated PK-PD targets for selected antimicrobial antibiotics. The PK-PD indices have been identified in in vitro dose fractionation studies and link drug exposure with bacterial killing. The PK-PD targets have all been identified in clinical studies primarily of critically ill patients, link drug exposure with clinical efficacy and may be utilised as a TDM target concentration. [MIC – minimum inhibitory concentration; $AUC_{0\text{-}24}$/MIC – ratio of area under the concentration time curve from 0-24 hours to MIC; C_{max}/MIC – ratio of

maximum concentration of antibiotic in a dosing interval to MIC; $T_{>MIC}$ – percentage of dosing interval that the antibiotic concentration is maintained above the MIC; C_{min} – minimum concentration of antibiotic in a dosing interval; *f* – free or fraction of drug not bound to plasma proteins].

Class of drug	**Optimal PK-PD index**	**PK-PD target**	**References**
Aminoglycosides	fC_{max}/MIC $fAUC_{0-24}$/MIC	C_{max}/MIC 8-30 AUC_{0-24}/MIC 70-100	(Rea et al. 2008) (Kashuba et al. 1999)
Carbapenems	$fT_{>MIC}$	40% - 75% $fT_{>MIC}$	(Ariano et al. 2005) (Li et al. 2007) (Taccone et al. 2012) (Lomaestro and Drusano 2005)
Cephalosporins	$fT_{>MIC}$	60-100% $fT_{>MIC}$ 95% $fT_{>4.3xMIC}$	(McKinnon et al. 2008) (Mouton and den Hollander 1994) (Tam et al. 2002) (Mariat et al. 2006) (Nicasio et al. 2009) (Muller et al. 2013)
Fluoroquinolones	$fAUC_{0-24}$/MIC fC_{max}/MIC	$fAUC_{0-24}$/MIC >30-250 C_{max}/MIC ≥8	(Drusano et al. 2004) (Ambrose et al. 2001) (Forrest et al. 1993) (Ambrose et al. 2003)
Linezolid	$fAUC_{0-24}$/MIC $fT_{>MIC}$	$fAUC_{0-24}$/MIC ≥85 85% $fT_{>MIC}$	(Alffenaar et al. 2010) (Rayner et al. 2003).
Penicillins	$fT_{>MIC}$	40-50% $fT_{>MIC}$	(Lodise et al. 2007) (Turnidge 1998) (Roberts et al. 2010) (Blondiaux et al. 2010)
Vancomycin	$fAUC_{0-24}$/MIC	AUC_{0-24}/MIC 86-460	(Moise-Broder et al. 2004) (Zelenitsky et al. 2013) (Kullar et al. 2011)