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Appropriate Antibiotic Dosage Levels in the Treatment of Severe Sepsis and Septic Shock

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Abstract Antibiotic treatment of critically ill patients remains a significant challenge. Optimal antibacterial strategy should achieve therapeutic drug concentration in the blood as well as the infected site. Achieving therapeutic drug concentrations is particularly difficult when infections are caused by some pathogens, such as *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus* (MRSA) and Gram-negative rods, because of their low susceptibility to antimicrobials. In sepsis, pharmacokinetics (PKs) of antibiotics are profoundly altered and may result in inadequate drug concentrations, even when recommended regimens are used, which potentially contribute to increased mortality and spread of resistance. The wide inter-individual PK variability observed in septic patients strongly limits the a priori prediction of the optimal dose that should be administered. Higher than standard dosages are necessary for the drugs, such as β-lactams, aminoglycosides, and glycopeptides, that are commonly used as first-line therapy in these patients to maximize their antibacterial activity. However, the benefit of reaching adequate drug concentrations on clinical outcome needs to be further determined.

Keywords Antibiotics · Antibacterial · Pharmacokinetics · Pharmacodynamic · Intensive care unit · Sepsis · Critically illness · Aminoglycosides · Glycopeptides · β-lactams · Dosage · Regimen

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Introduction: Principles of Antibiotic Prescription for the Critically Ill Patient

Sepsis is a major healthcare problem, being one of the most important reasons for admission to Intensive Care Units (ICUs) and resulting in high morbidity and mortality, which rises up to 50% in case of septic shock [1–3]. Along with effective volume replacement and prompt hemodynamic optimization [4], compelling evidence suggests that an early and appropriate antibiotic therapy is mandatory in the management of septic patients. The impact of timing in antibiotic prescription has been shown in several studies [5, 6] and delayed antimicrobial administration increased the risk of death in hypotensive patients by 7% for every additional hour without antibiotics [7]. Also, the treatment must effectively target the responsible pathogen. Initial administration of an ineffective antimicrobial against the isolated strain is associated with prolonged hospital stay and poor prognosis, while subsequent adjustment of therapy based on antimicrobial susceptibility had no impact on mortality [8•, 9, 10]. Pathogens

involved in nosocomial infections, such as *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, methicillin-resistant *Staphylococcus aureus* (MRSA) and extended spectrum β-lactamase (ESBL) producing Gram-negative bacteria (GNB), are associated with a greater probability of inappropriate antibiotic therapy [8•, 11]. Empirical treatment should therefore be directed against all the pathogens potentially involved in the suspected infection, taking into account patients' history and the community/hospital epidemiology. In hospital-acquired infections, the combination of broad-spectrum β-lactams, in association with aminoglycosides and/or glycopeptides, is recommended [4].

Antibiotic treatment is appropriate not only because it is in vitro active against the isolated pathogen, given as early as diagnosis of infection is made and according to the site of infection, but also because the selected regimen offers optimal killing drug activity [12]. The importance of an adequate dose has been highlighted in several studies. In a controversial meta-analysis of 57 randomized clinical trials having used broad-spectrum β-lactams for the treatment of different infections, a 26% increase in 30-day mortality was observed for patients treated with cefepime in comparison with those treated with other molecules [13]. These results were not determined by differences in patients' severity, neutropenia or minimal inhibitory concentrations (MICs) for the studied drugs. Among all, one of the possible explanations was that the used regimen of cefepime (ie, 1–2 g q12h) could have resulted in insufficient drug concentrations to achieve clinical efficacy. This hypothesis was supported by Monte Carlo simulation, based on ESBL MICs, in which a cefepime regimen of 2 g every 8 h was sufficient to provide adequate concentrations in nearly 70% of the strains, while lower dosages (1 g every 12 h or 2 g every 12 h) resulted in only 27% and 50% of therapeutic drug levels, respectively [14]. Insufficient concentrations may also explain the high mortality rates associated with infections due to less susceptible GNB when treated with broad-spectrum β-lactams [15, 16•]. These data emphasize that therapeutic failure could be related to the low probability of achieving target serum concentrations, especially if the strain is susceptible but with high MIC to the drug at the laboratory testing. These less susceptible pathogens represent the main therapeutic challenge for clinicians, in terms of appropriate choice and optimal dosing.

How Can Sepsis Affect Antibiotic Concentrations?

Antimicrobial dosages used in sepsis are derived from pharmacokinetic (PK) data obtained from healthy volunteers, or less severely ill patients, without taking into account the PK changes occurring during sepsis that reduce antibiotics efficacy [17, 18]. In sepsis, increased cardiac output and interstitial fluid shifts, associated with increased capillary leakage, induce a larger volume of distribution (Vd), which may decrease antibiotic plasma levels [19]. Also, peripheral effusions, such as in the pleura or the abdomen, the use of drains or extra-corporeal circuits may further change the distribution of antibiotics. Decreased protein binding, as observed with hypoalbuminemia, can result in higher free-drug concentration and increased total clearance (CL) [20]. In the absence of significant organ dysfunction, this hyper-dynamic status can also increase renal blood flow and supranormal creatinine clearance, resulting in elevated antibiotic elimination, may be observed [21•]. On the other hand, organ dysfunction (ie, renal or hepatic) may develop and contribute to alter drug metabolism and CL, leading to drug accumulation with possible side effects [19]. In these situations, renal replacement therapy is often needed and the additional antibiotic removal must be considered to adapt the dosing and to maintain therapeutic concentrations [22]. Finally, infections, especially when acquired in the ICU, are often caused by more resistant pathogens, which require higher drug concentrations to be treated [23]. All these PK changes mainly affect hydrophilic compounds, such as aminoglycosides, β-lactams and glycopeptides, as they have a small Vd (limited to extracellular fluids) and are more likely to be excreted unchanged by the kidney [19]. Thus, adequate dosing for these drugs should be reconsidered to avoid underdosing with potentially worse outcome, but also overdosing with related toxicity.

Pharmacokinetic and Pharmacodynamic Principles to Optimize Antibiotic Activity

Pharmacokinetics refers to the study of changes in drug concentrations over time [24•]. In addition of Vd and CL, the peak concentration obtained after a single dose (C_{max}), the lowest concentration before the following administration (C_{min}) and the area under the serum concentration time curve (AUC) are generally calculated to determine the adequacy of drug levels. Pharmacodynamics (PD) relate PKs to the ability of antibiotics to kill or inhibit the growth of micro-organisms [24•]. The parameter that is used to quantify the response of a pathogen to an antimicrobial is the MIC, which represents the antibiotic concentration resulting in inhibition of visible growth under standard conditions [25]. Thus, PD parameters include the time that serum concentrations remain above the MIC (T>MIC), the ratio of the peak concentration to the MIC (C_{max}/MIC) or of the AUC to the MIC (AUC/MIC). Knowledge of the antibiotic PK/PD properties is essential for selecting the appropriate regimen [24•] (Fig. 1). Also, in critically ill patients, therapy should usually target MIC of problematic pathogens, such as *Enterobacteriaceae* and *Pseudomonas*

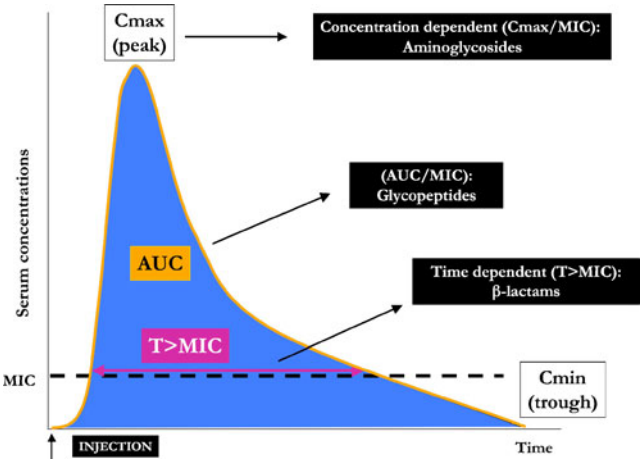

Fig. 1 Pharmacokinetic and pharmacodynamic parameters of β-lactams, aminoglycosides and glycopeptides on a concentrations vs. time curve. *AUC* Area under the curve; *Cmax* peak concentration obtained after a single dose; *Cmin* the lowest concentration before the following administration; *MIC* minimal inhibitory concentration

aeruginosa, which are associated with the highest morbidity and mortality [26, 27].

β-lactams

In vivo animal studies have demonstrated that β-lactams have a slow continuous kill characteristic that is almost entirely related to the time during which serum concentrations exceed the MIC (T>MIC) for the infecting organism [28, 29]. This effect is independent of peak levels so that, to optimize this PD end-point, β-lactams regimens are generally administrated in multiple daily doses [24•]. In vitro killing curve studies have shown that β-lactams killing activity was rapidly saturated at concentrations corresponding to 4 times the MIC, so that greatly increasing antibiotic concentrations (ie, above 8 or 16 times the MIC) did not kill bacteria more rapidly or more extensively [30]. Furthermore, β-lactams do not exert post antibiotic effects (PAE, defined as the continued inhibition of bacterial growth even for drug concentrations below the MIC) on *Streptococcus* spp. and GNB, with the exception of carbapenems and a better control of the infection is achieved when drug concentrations are maintained above the MIC for extended period of time [31]. Unfortunately, there are no data comparing the efficacy of different therapeutic end-points in the human setting; target β-lactams concentrations above the MIC as well as the time concentrations should be maintained above MIC over the dosing interval remain controversial. In animal models, maximal bacterial killing was obtained with drug concentrations of 4–5 times the MIC; however, higher concentrations of 6 times the MIC were necessary to treat some bacteria, such as *P. aeroginosa* [32]. Microbiological success, but not clinical cure, was significantly correlated with the proportion of the dosing interval when cefepime concentrations exceeded 4 times the MIC in human infections [33]. On the other hand, it has been suggested that, in the absence of any PAE, maximum killing is achieved when T>MIC approaches 90% to100% of the dosing interval [34]. This may be especially appropriate in patients with compromised host-defences, including critically ill patients [35]. In 76 patients treated with cephalosporins for serious bacterial infections, patients with T>MIC of 100% had significantly greater clinical cure and bacteriological eradication than patients with T>MIC of <100% [36••]. When the drug has in vivo PAE, such as for carbapenems, adequate antimicrobial activity is obtained even when T > 40% to 50% of the dosing interval [24•, 34]. Clinical studies did not provide further evidence supporting this strategy, because drug concentrations were not routinely measured, or infections were due to bacteria with low MICs. Based on these limited data, we suggest that to deliver optimal β-lactam treatment for GNB infections, the concentration of the drug should be above 4 times the MIC for at least 70%, 50% and 40% of the dosing intervals for cephalosporins, penicillins and carbapenems, respectively (Table 1) [53].

Aminoglycosides

The C_{max}/MIC ratio is considered as the parameter that best characterizes the in vivo exposure of the strain to serum aminoglycoside concentrations [37, 38]. In a retrospective study, C_{max}/MIC between 8 and 10 was the major determinant for optimal antibacterial activity and clinical response (Table 1) [39]. Also, target Cmax/MIC ratio achieved in the early therapy increased the probability of a rapid therapeutic response for GNB pneumonia [40]. Because of this PD characteristic and a significant PAE, a single daily administration is the optimal solution to increase aminoglycoside antibacterial activity [24•]. Several studies and meta-analyses have suggested that this regimen is as effective, if not superior, to multiple daily administrations and with a lower risk of toxicity [41, 42]. In addition, this strategy was shown to be associated with a lower probability to select resistant strains [24•]. The prescription of aminoglycosides in critically ill patients is complex because of the narrow therapeutic index of these drugs. Potential renal, vestibular and neuromuscular toxicity can occur in the early or late phase of aminoglycoside therapy, with a wide spectrum of severity [43]. The risk of renal dysfunction is increased with concomitant hypovolemia, preexisting renal disease, nephrotoxics and advanced age [44]. Cumulative dose, especially when there are persistent elevated trough concentrations, is also associated with an increased risk of renal toxicity so that the monitoring of C_{min} is advocated to minimize drug side effects [24•].

Table 1 Recommended and PK-adjusted regimens for aminoglycosides, broad-spectrum β-lactams and vancomycin. Dosages are proposed in case of normal renal function and to target less susceptible strains. Daily regimens of aminoglycosides will depend on the C_{max}/MIC ratio obtained with the previous administrations and on the C_{min}. Continuous infusion is applied when drug is administered over 24 h. Extended infusion is scheduled as 3 to 4-hour administration for piperacillin and 3-hour administration for meropenem

	Recommended loading dose	Recommended daily dose	PK target	PK adjusted loading dose	PK adjusted daily dose
Amikacin	15 mg/kg	–	C_{max}/MIC > 8–10	25–30 mg/kg	–
Tobramycin	5–7 mg/kg	–	C_{max}/MIC > 8–10	8–9 mg/kg	–
Gentamycin	5–7 mg/kg	–	C_{max}/MIC > 8–10	8–9 mg/kg	–
Cefepime	2 g	2 g/8 h	70% T > 4 x MIC	2 g	6 g CI
Ceftazidime	2 g	2 g/8 h	70% T > 4 x MIC	2 g	6 g CI
Piperacillin	4 g	4 g/6 h	50% T > 4 x MIC	4 g	4 g q6h ED
Meropenem	1 g	1 g/8 h	40% T > 4 x MIC	1 g	1–2 g/8 h ED
Vancomycin	15 mg/kg	15 mg/kg/12 h	C_{min} > 15–20 μg/mL (II) C_{min} > 20–30 μg/mL (CI)	35 mg/kg in 4 h	30–40 mg/kg CI

CI continuous infusion; *C_{max}* peak concentration; *II* intermittent infusion; *MIC* minimal inhibitory concentration; *T>MIC* time above the MIC.

Glycopeptides

Glycopeptides antibiotics include vancomycin and teicoplanin. Although these two drugs have similar characteristics, vancomycin is considered the drug of choice in the therapy of serious Gram-positive (GPB) infections in ICU. Significant controversy has occurred in recent years regarding the efficiency by which vancomycin kills GPB and the potential misuse of the drug [45]. Some in vitro studies suggested that C_{max}/MIC ratio correlated with drug efficacy in non-neutropenic animals [46], while others suggested that the bactericidal activity of glycopeptides could be driven by either T>MIC or AUC/MIC [47, 48]. In humans, Moise et al. [49] reported that an AUC/MIC value ≥350 was an independent factor associated with clinical success in patients with *Staphylococcus aureus* proven lower respiratory tract infection. As it may be difficult to obtain multiple serum vancomycin concentrations to determine the AUC, C_{min} monitoring has been recommended as the most accurate and practical method to adjust vancomycin regimens [50]. Recent guidelines suggested a C_{min} more than 15–20 μg/mL to ensure efficacy of the drug (Table 1) [51••]. Nevertheless, the efficacy of vancomycin is limited by the poor penetration into solid organs, particularly the lung or central nervous system [45]. Moreover, a significantly higher mortality rate is associated with MRSA bacteraemia due to strains with MICs >1 μg/mL, when vancomycin is used [52]. Alternatively to other drugs, such as rifampicin, linezolid or tigecycline, higher C_{min} >20 μg/mL has been advocated in these situations [51••]. An even higher concentration of vancomycin, up to 40 μg/mL, has been suggested to optimize drug efficacy for MRSA with MIC ≥2 μg/mL [53]. However, when increasing the dose of vancomycin, toxicity may occur and some studies have shown that drug levels above 28 μg/mL were associated with a greater risk of renal dysfunction, especially if other potential nephrotoxics, such as aminoglycosides or amphotericin, are coadministered [54].

How to Optimize Antibiotic Administration in Critically Ill Patients

β-lactams

This class of antibiotics includes penicillins, monobactams, cephalosporins, and carbapenems, which are active against most organisms recovered from ICU patients. Studies on serum concentrations of broad-spectrum β-lactams have already reported that drug levels are insufficient in patients with severe infections to treat less susceptible strains. Cefepime (2 g taken every 12 h) concentrations were more than 70% above target concentrations in less than half of the patients with sepsis [55] and were adequate only for MICs of 4 μg/mL in post-operative infections [56]. Septic patients with normal renal function had serum cefepime and ceftazidime levels below therapeutic levels after a few hours in most cases [57, 58]. Ceftazidime trough concentrations were below the median MIC of *Pseudomonas aeruginosa* in more than half of the patients in another study [59]. In only one study, ceftazidime levels were above the MIC of the isolated pathogens for more than 90% of the time interval; however *Pseudomonas* was isolated in only 4 of 16 patients [60]. Piperacillin concentrations were above therapeutic levels for most of the time interval in patients with sepsis [61•] or nosocomial pneumonia [62]. On the other hand, serum drug concentrations of meropenem were adequate in most of the studies in critically ill patients. In severe infections associated with bacteremia, mostly after cardiac surgery, meropenem had adequate serum concen-

trations for at least 50% of the time in patients with normal and impaired renal function [63]. In patients with ventilator-associated pneumonia, mean T >4 × MIC for *Pseudomonas* was reported as 52% in one study [64] and 46% in another [65]. Nevertheless, most of these studies excluded severely ill patients with septic shock and those with multiple organ failure, limiting the generalization of their results to other populations of critically ill patients. The number of patients was also limited and analyses concerned only the steady-state of the disease. We have recently shown in a prospective multicenter study that serum levels obtained after the first dose of either piperacillin-tazobactam, ceftazidime, or cefepime were insufficient to empirically treat less susceptible pathogens in the early phase of severe sepsis and septic shock, as 15/27 patients for piperacillin-tazobactam, 13/18 for ceftazidime, and 16/19 for cefepime did not attain the target PD end-point [66••]. Nevertheless, 12/16 (75%) of the patients receiving meronem achieved adequate serum concentrations. Our study focused on a more severe population of patients, suffering from severe sepsis and septic shock, with higher mortality and morbidity rates than less severely ill ICU populations [3]. In another recent prospective study, β-lactams levels monitoring was routinely applied in 236 critically ill patients' management. Dose adjustment was required in 175 (74%) of the patients, with 119 of those (50%) requiring dose increases during the early phase of infection therapy [67••]. The increase of drug regimens was more frequent for difficult-to-treat pathogens, such as *Pseudomonas aeruginosa*, *Enterobacter* and *Klebsiella spp*. or MRSA, suggesting again that these represent the target pathogens for which β-lactams dose adjustment is necessary to improve blood drug concentrations. Moreover, low plasma levels can contribute to lower than expected β-lactam concentrations in the extracellular, bronchial or peritoneal fluid [68–70] with potentially reduced antimicrobial delivery to the target tissues. In view of these results, in the early phase of sepsis, broad-spectrum β-lactams should be administered more frequently or in doses larger than suggested in non-septic patients, with a dramatic increase of therapy costs. As such, according to population modelling simulation, continuous or extended β-lactam infusions are required to optimize pathogen exposure to bactericidal concentrations of these drugs (T>MIC) [24•] (Table 1). Continuous infusion (CI) of β-lactams rapidly achieved target concentrations even for less susceptible GNB [71, 72]. However, clinical data that have shown a better outcome using this strategy have come just from retrospective studies in critically ill populations with pneumonia [73, 74]. Further studies are needed to assess the influence on morbidity and mortality of CI strategy, especially in patients with sepsis and in infections caused by multiresistant pathogens.

Importantly, over-dosing and toxicity of β-lactams could also be a concern when high dosages are used, so that drug monitoring is mandatory in this setting [24•]. In 10% of ICU patients with renal dysfunction receiving cefepime, serum drug accumulation occurred despite dosage adjustments and resulted in non-convulsive seizures, disappearing after drug discontinuation [75••]. Roberts and al. [67••] reported that a dose reduction was applied in 24% of ICU patients when monitoring was routinely performed. Thus, if high or CI regimens of β-lactams are necessary to rapidly achieve therapeutic drug levels for difficult-to-treat pathogens, PK abnormalities may change or resolve during time and, in these later circumstances, dose adjustments are needed.

Aminoglycosides

Aminoglycosides (amikacin, tobramycin and gentamycin) are often given as part of empiric therapy for severe sepsis and septic shock, especially if *Pseudomonas aeruginosa* infection is suspected. Their use is further supported by the emergence of multidrug-resistant bacteria and the lack of new drugs active against these micro-organisms [76]. Meta-analyses have shown limited and conflicting benefits from this combination therapy [77, 78]. However, the paucity of trials including patients with severe sepsis and septic shock precludes any recommendations in this setting and the different amikacin doses and regimens used may have lead to inadequate drug concentrations. C_{max} concentration is determined by the administered dose and by the Vd [24•]. The Vd of aminoglycosides is largely increased in critically ill patients when compared to healthy volunteers and patients with mild infections and an association between sepsis severity, estimated by the APACHE II score, serum albumin or adrenergic support with aminoglycoside Vd has been described [79, 80]. Giving recommended aminoglycoside regimens, the peaks obtained were largely below the desired concentrations to treat *Pseudomonas aeruginosa* and resistant GNB, suggesting that higher doses of these drugs should be administered to achieve optimal C_{max} [79, 81]. Most of the studies on aminoglycosides in ICU patients had potential biases related to limited patient sample size, retrospective analysis or exclusion criteria, such as septic shock, APACHE II score >35, liver cirrhosis or acute renal failure. We have recently shown that a loading dose of 25 mg/kg of amikacin is necessary to achieve optimal peak concentrations in a prospective cohort of septic patients with several co-morbidities, high disease severity and multiple organ dysfunctions, resulting in an ICU mortality rate of 40% [82••]. An even higher dose may be necessary in some patients for whom peak still remains below the desired level (Table 1). Simulation with a standard regimen (15 mg/kg) of amikacin resulted in insufficient peak concentrations in more than 90% of patients, thus confirming the need to increase amikacin regimen to optimize C_{max} in septic patients. Assuming the

threefold to fourfold factor for converting the doses of amikacin in gentamicin and tobramycin, suggestion for the use of higher doses were reported for these two aminoglycosides (8–9 mg/kg) in patients with septic shock [83••, 84]; however, a dose higher than 7 mg/kg has not been prospectively validated for these drugs.

High regimens need also MIC and C_{min} measurement to optimize subsequent dosages and avoid drug accumulation. In case of renal impairment, aminoglycoside CL is reduced and drug administration should be significantly delayed [24•]. If using higher than recommended regimens can enhance aminoglycoside-related renal dysfunction has not been studied yet; however, targeting optimal amikacin peaks resulted in the same incidence of nephrotoxicity compared with conventional treatment [85], as long as individualized PK drug dosing was performed to allow a necessary drug-free period. Moreover, if aminoglycosides are the only available therapy for pan-resistant pathogens with high MIC for these drugs, the use of continuous renal replacement therapy (RRT) could enhance extra-renal clearance of the drug, allow daily drug administration and result in effective clinical cure for these severe infections [86].

Glycopeptides

Vancomycin is effective against GPB, including *Staphylococcus aureus* and *epidermidis* or *Enterococcus spp*. Higher than recommended doses of vancomycin were necessary to optimize drug concentrations and rescue patients from septic shock due to GPB [87•]. Also, an increase in daily vancomycin regimen was necessary to achieve recommended C_{min} in critically ill trauma patients with MRSA pneumonia and normal renal function [88•]. Administration of the conventional dose of vancomycin (15 mg/kg of body weight every 12 h) would probably fail to achieve therapeutic drug concentrations in the majority of critically ill patients [89, 90]. Therefore, a CI with a 30 mg/kg daily dosage has been proposed to optimize PD vancomycin (Table 1) [90]. However, the question of whether intermittent dosing or CI is better to improve vancomycin efficacy remains unanswered. In patients receiving vancomycin for osteomyelitis, there was a trend to better outcome in those treated with CI than those with conventional regimens. Also, less adverse drug reactions necessitating discontinuation of treatment were noticed [91]. Wysocki et al. [92] compared CI and intermittent dosing of vancomycin in 160 patients with severe MRSA infections and found no significant differences in clinical efficacy. However, faster time to achieve target drug concentrations, lower daily dose and reduced therapy costs were reported for the CI strategy. Rello et al. [93] suggested a clinical superiority of CI of vancomycin in a subgroup of patients with ventilator-associated pneumonia due to MRSA. Finally, a slower onset of nephrotoxicity in patients receiving vancomycin by CI, despite similar duration of treatment and cumulative dose than intermittent regimen, was reported [94]. While all these potential advantages for CI of vancomycin have been described, the adequate regimen to rapidly achieve target concentrations (20–30 μg/mL) in critically ill patients is still unclear. The need for higher doses of CI vancomycin has been shown in two studies [95••, 96••]; however drug concentrations were measured only at steady-state and the adequacy of this strategy in the first days of treatment remained unknown. Using Monte Carlo simulation, we found that higher than recommended loading (35 mg/kg) and daily (30–40 mg/kg if normal renal function) doses of CI vancomycin were necessary to achieve therapeutic serum concentrations in the early phase of sepsis [97••]. However, this strategy needs to be prospectively validated and its impact on drug-related toxicity further determined.

Other Conditions

Acute renal failure is a common complication of sepsis. In this setting, the use of continuous RRT can further alter the PK of antibiotics. These PK changes depend on several variables, such as the ultrafiltrate and dialysate rates, dialysate concentrations and the type of membrane used, each of these introducing additional variability in expected drug concentrations [24•]. The most recent recommendations on antibiotic dosing during continuous RRT [22] were established using evidence from studies including a limited number of patients, with varying inclusion/exclusion criteria and receiving different types of RRT. Serum measurements were usually performed at steady state, which also limits the extrapolation of results to the early phase of sepsis, during which patients are often hemodynamically unstable. Physiologic alterations associated with increased body weight also affect antibiotic PKs. This is due to the variable penetration of these drugs into adipose tissue. Previous studies have recommended dosing weight correction factors to normalize antimicrobial regimens in overweight patients with less serious infections, but not having sepsis [98]. Finally, significant PK alterations have been also described in burned patients or liver cirrhosis [24•]. All these situations require drug levels monitoring and antibiotic dose adjustment.

Conclusions

Monitoring serum antibiotic concentrations is important in critically ill patients. Drug underdosing is frequent in the early phase of therapy and when less susceptible strains are targeted. On the other hand, possible side effects associated with antibiotic overdosing, including neurological distur-

bances or renal failure, may occur and need to be avoided. The intention of this review was not to provide definitive dose recommendations for broad spectrum β-lactams, aminoglycosides and vancomycin.

We underlined that the use of higher than recommended regimen is necessary to optimize PD properties of these drugs and potentially improve their clinical efficacy. Clearly, systematic clinical PK/PD studies are required to evaluate the beneficial effects of this strategy on the outcome of septic patients.

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•• Of major importance

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