Infections occurring in intensive care units (ICU) are associated with high morbidity and mortality rates. This can be partly attributed to the fact that critically ill patients are highly susceptible to infections due to co-morbidities and the impairment of mechanical and immunological protective barriers. Indeed, critically ill patients could be compared to an unbalanced system because of their variable and instable clinical status, such that they require prompt and continuous therapeutic adjustments to maintain organ function, homeostasis and clinical stability. In addition, ICU facilities themselves have become a reservoir of aggressive and multi-resistant pathogens, while the availability of effective antibiotics is often very limited, a fact related mainly to the extensive and inappropriate use of antimicrobial agents. Methicillin-resistant Staphylococcus aureus (M RSA), and multi- or pan-drug-resistant Pseudomonas aeruginosa, Acinetobacter baumannii and Enterobacteriaceae are characteristic examples of aggressive pathogens that the ICU physician must confront in everyday clinical practice. Moreover, the inappropriate use of antibiotics, together with the severity of the underlying conditions of critically ill patients, is responsible for poor clinical outcome.
Given these factors, optimizing antibiotic efficacy in the ICU setting has become mandatory. This target can be reached by taking best advantage of the pharmacokinetic/pharmacodynamic (PK/PD) properties of antibiotics. Indeed, it has been demonstrated that PK/PD properties are major determinants of in vivo efficacy of antibiotics, and data from in vitro and animal studies have demonstrated that incorrect manipulation of PK/PD parameters may lead to the emergence of resistance.9 These findings have also been corroborated in the clinical setting. For example, Thomas et al. have shown that an AUC0-24/MIC ratio less than 100 was strongly associated with the selection of antimicrobial resistance in a cohort of acutely ill patients treated with ciprofloxacin and various beta-lactams.10

Over the years, the literature has provided extensive information about the PK/PD properties of single antibiotics; however, new PK/PD issues that have recently emerged render antibiotic therapy even more complex and controversial, especially in the ICU setting.11 In this article, some current issues concerning the PK/PD properties of antibiotics commonly used for the treatment of infections in the ICU setting will be discussed, with a major emphasis on the route of administration and the minimum inhibitory concentration (MIC) values. It is true that a few more potent antimicrobial agents (e.g., linezolid and tigecycline) have become available for the treatment of severe ICU infections during the last years. However, these innovations do not compensate for limited availability of effective antimicrobial agents. Due to the emergence of multi-drug resistance pathogens, clinicians are likely to switch to new antimicrobial agents; however, the problem of antimicrobial resistance is still evolving. The emergence of multi-drug resistant pathogens can be averted or delayed if clinicians take into account the particular PK/PD characteristics of the commonly administered agents and consider pathogen susceptibility patterns.8-10 For these reasons, this review will focus on the PK/PD aspects of commonly used antimicrobials in the ICU setting, such as beta-lactams, vancomycin and aminoglycosides, and will provide particular examples on how the proper administration of older agents and the inclusion of newer ones in de-escalation strategies might become a powerful tool in dealing with the problem of emerging antimicrobial resistance. Prior to discussing PK/PD issues related to antimicrobial treatment of the critically ill, a brief introduction to basic PK/PD principles of antimicrobial chemotherapy will be provided.

Basic PK/PD principles of antimicrobial chemotherapy

Pharmacokinetics aims to quantify the time course of the serum level of an agent by employing, among others, parameters such as the drug peak serum (Cmax), steady-state serum (Css) trough serum level (Cmin), volume of drug distribution (Vd) and the area under the serum concentration-time curve (AUC). On the other hand, pharmacodynamics quantifies the activity of an antimicrobial agent by integrating its PK parameters with the MIC for a particular pathogen. From the PD point of view, antibiotics can be categorized based on their mode of bacterial killing and the presence of a post-antibiotic effect. Thus, the pattern of bacterial killing of an antibiotic can be concentration-dependent if higher concentrations of the agent result in more extensive elimination of the pathogen or time-dependent, if the effectiveness of bacterial killing depends upon the duration of pathogen exposure to the agent. The term “post-antibiotic effect” (PAE) refers to the time required by the pathogen to resume normal growth following exposure to the agent.12,13 Therefore, antimicrobial agents can be classified basically into two categories. The first category includes drugs that exhibit concentration-dependent killing in combination with a prolonged post-antibiotic effect (e.g., aminoglycosides, fluoroquinolones); the best predictors of efficacy for this class of agents are the peak drug concentration divided by the MIC (Cmax/MIC) and/or the AUC at 24 hours in relation to MIC (AUC0-24/MIC).14,15 The second category includes drugs that exhibit a time-dependent pattern of killing with minimal or moderate post-antibiotic effect (e.g., beta-lactams, macrolides, glycopeptides); for this category, the time the concentration of antibiotic remains above the MIC (T>MIC) is an important determinant of efficacy.16,17 The parameters most strongly correlated to clinical
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PETROSILLO

Table I.— Principal pharmacodynamic/pharmacokinetics characteristics of antimicrobials

A. According to the pattern of antimicrobial killing:

1. Time-dependent antibiotics (Beta-lactams, glycopeptides, linezolid, quinupristin/dalfopristin and the glycylcyclines). The time that free antimicrobial concentrations remain above the MIC (T > MIC) is the PK/PD index correlating with efficacy. PAE is minimal (Beta-lactams) or moderate (glycopeptides, linezolid, quinupristin/dalfopristin, glycylcyclines).

2. Concentration-dependent antibiotics (aminoglycosides, fluoroquinolones, daptomycin). The peak concentration/minimum inhibitory concentration (Cmax/MIC) ratio and/or the area under the concentration-time curve at 24 h/MIC (AUC0–24/MIC) ratio are the best PK/PD parameters correlating with efficacy. Moreover, there is a prolonged post-antibiotic effect (PAE).

B. According to solubility:

1. Hydrophilic antibiotics (Beta-lactams including penicillins, monobactams, cephalosporins and penems, glycopeptides, aminoglycosides): their volume of distribution is limited to the extracellular space and their plasma and interstitial concentrations may decrease due to fluid extravasation. They are inactive against intracellular germs, and have renal elimination.

2. Lipophilic antibiotics (Macrolides, fluoroquinolones, tetracyclines and glycicyclines, oxazolidinones, rifampicin, dorampanol). They have a large volume of distribution, and the dilution of interstitial fluids is less relevant compared to hydrophilic antibiotics. They are active against intracellular germs and are mainly eliminated by the liver.

Efficacy (Table IA). Furthermore, antibiotics can be classified as either hydrophilic or lipophilic based on their ability to cross cellular membranes and the resultant volumes of distribution (Table IIB).12, 13

Influence of critical illness on PK/PD parameters of antibiotics

Critical illness is characterized by significant alterations in 1) fluid distribution and homeostasis; 2) hemodynamic parameters and microcirculation; and 3) organ function scores. These abnormalities may affect PK/PD parameters in a variety of unpredictable ways.

Antibiotic distribution volume

Fluid distribution and homeostasis undergo significant derangements in critically ill patients via three main pathophysiologic processes: 1) fluid extravasation, as in sepsis, trauma, hypoalbuminemia, external fluid overload, renal and cardiac failure; 2) fluid loss, as in surgical drainages and burns; and 3) local fluid overload, as in pleural infusion and ascites. These disturbances result in an increased Vd for hydrophilic antibiotics with a subsequent decrease in their plasma concentration.21 Lipophilic drugs, on the other hand, are not significantly influenced by these alterations due to their large volumes of distribution.13

Antibiotic excretion and elimination

The cardiac index may be normal or even increased in severe sepsis and septic shock, particularly following fluid resuscitation.13 Thus, unless organ dysfunction ensues, renal artery blood flow is also increased, resulting in the enhanced delivery and excretion of hydrophilic and moderately lipophilic antibiotics,11 decreasing their half-life. In addition, hypoalbuminemia, which is frequently encountered in critically ill patients, may further augment antibiotic clearance by increasing the free fraction of protein-bound antibiotics (e.g., telcoplanin, ceftriaxone).13 Lastly, the administration of drugs with hemodynamic modes of action (such as dopamine or dobutamine) or diuretics may also influence the glomerular filtration rate and consequently alter antibiotic clearance.13

On the other hand, advanced critical illness is characterized by multiple organ failure, with the kidneys and the liver commonly involved in this process. Acute kidney damage is very common in critically ill patients22 and may prolong the elimination half-life of the renally-excreted hydrophilic and moderately lipophilic drugs, leading to an accumulation of toxic metabolites. Furthermore, continuous or intermittent renal replacement therapy, a measure commonly utilized in ICUs for the management of renal failure, can significantly alter antibiotic clearance via a variety of mechanisms related to the mode of treatment, exchange rates,
membrane properties and duration of therapy. On the other hand, the elimination of lipophilic antibiotics is mainly influenced by liver dysfunction. However, the liver has a considerable functional reserve and dose adjustments are not usually required except in more severe cases of liver failure. However, the impact of the liver support systems on antimicrobial PK/PD parameters remains undefined.

### Tissue penetration

Septic shock may significantly affect antibiotic distribution to the tissues by decreasing their concentrations at the target site to subinhibitory levels even while the achieved plasma drug concentrations would still be considered “effective”. This situation, though still largely unexplored, could account for clinical treatment failures.

### Continuous/prolonged or intermittent infusion of antimicrobials for critically ill patients in the ICU setting?

Continuous/prolonged administration of antibacterial agents with a time-dependent pattern of killing is considered a plausible and enticing therapeutic option. Kasiakou et al. have evaluated PK/PD data provided from 17 randomized controlled trials (most of them involving critically ill patients) that compared continuous and intermittent modes of administration of antibacterials with time-dependent action (beta-lactams or vancomycin). They found that theCss achieved with a continuous infusion strategy was higher than the Cmax achieved via intermittent infusion in all 14 studies that provided relevant data; furthermore, the T>MIC was higher with continuous infusion in 3 out of 6 studies that assessed this issue. They concluded that the continuous infusion strategy might be a better option for infections caused by bacteria with high MIC values, a problem relevant to the ICU setting. In addition, the same group has evaluated clinical outcomes in a meta-analysis of randomized controlled trials that compared continuous and intermittent infusions of various antimicrobial agents (beta-lactams, aminoglycosides and vancomycin). This study showed a tendency towards a better clinical outcome for the continuous infusion arm (OR 0.73, 95% CI 0.53-1.01) that reached statistical significance when studies which used same total daily doses in both arms were analyzed separately (OR 0.70, 95% CI 0.50-0.98; P=0.004); in addition, no differences in mortality or nephrotoxicity were noted. This issue was revisited recently by Roberts et al. in a meta-analysis involving 14 RCTs investigating continuous or prolonged versus intermittent administration of beta-lactam antibiotics. This study failed to find any statistically significant difference in clinical cure or mortality rates in favor of the prolonged or continuous administration strategy. However, this result can also be attributed to differences in total doses between the two arms, a failure to reach clinically relevant PK/PD therapeutic targets in individual studies and the inclusion of a diverse population of patients. Indeed, critically ill patients might represent a separate subgroup that could particularly benefit from prolonged or continuous infusion of antibacterial agents with time-dependent modes of action.

Some issues concerning antibiotics that exhibit a time-dependent pattern of killing and are commonly used in the ICUs will be analyzed further.

### Vancomycin

Vancomycin has played a major role in the treatment of bacterial infections caused by multidrug-resistant gram-positive pathogens, most notably methicillin-resistant Staphylococcus aureus (MRSA). Vancomycin exhibits a time-dependent mode of bacterial killing with a moderate post-antibiotic effect. Knudsen et al. demonstrated that T>MIC and Cmax are the parameters that may predict the clinical efficacy of a single-dose glycopeptide treatment. Furthermore, a seminal paper by Moise-Broder et al. emphasized the importance of vancomycin AU C0-24/MIC in predicting clinical success (>350) and bacterial eradication (>400). However, vancomycin penetrates poorly into the tissue, and concerns have been raised regarding its clinical efficacy against deep-seated infections. For instance, the “Tarragona strategy” strongly discourages the use of vancomycin for the treatment of ventilator-associated pneumonia (VAP) caused by MRSA and other gram-positive pathogens. Therefore, some authors propose that
severe infections caused by MRSA should be managed with a rapid achievement and maintenance of trough (minimum) plasma concentrations (\(C_{\text{min}}\)) of 15 to 20 mg/L.\(^{36, 37}\)

Commonly used vancomycin administration schedules often fail to achieve a \(C_{\text{min}}\) of more than 15 mg/L.\(^{38, 39}\) Indeed, Kitzis et al. have demonstrated that the administration of vancomycin in two or four daily doses often failed to achieve a \(C_{\text{min}}\) of more than 15 mg/L.\(^{38}\) In this study, \(C_{\text{min}}\) was <10 mg/L in 45.1% of 780 patients at 36 to 48 hours following the commencement of vancomycin treatment.\(^{38}\) Therefore, alternative regimens that can optimize the pharmacodynamics of vancomycin have been proposed, including higher intermittent daily dosages\(^{37, 40}\) or continuous infusions.\(^{41}\)

Administration of larger intermittent daily dosages of vancomycin can achieve a \(C_{\text{min}}\) of 15 to 20 mg/L in most patients, but the risk of nephrotoxicity is unacceptable, especially when the dose is greater than 4 g per day.\(^{42}\) Therefore, this choice would be an unlikely one for ICU physicians.

In an attempt to assess the optimal dosing schedule required to achieve a vancomycin steady-state concentration above 15 mg/L in patients treated with continuous infusion (preceded by a loading dose), Pea et al. developed a formula correlating vancomycin and creatinine clearance based on retrospectively collected data from 70 critically ill patients.\(^{41}\) This formula was further validated in a prospective cohort of 63 critically ill patients and it performed reasonably well (\(r=0.80, P<0.001\)).\(^{41}\) Based on their results, the authors proposed dose-clearance nomograms to assist clinicians in targeting vancomycin steady-state concentrations of 15 and 20 mg/L in critically ill patients.\(^{41}\) However, as the authors correctly note that the Cockcroft-Gault formula\(^{43}\) employed to calculate creatinine clearance in their study may overestimate the renal function in patients with prolonged hospital stays,\(^{44}\) invalidating the applicability of the proposed nomograms to these patients. In addition, they acknowledge that the dosing schedule they propose might not be reliable in the case of functionally anephric patients on dialysis and for patients with creatinine clearance estimates of <10 mL/min.\(^{41}\)

Beta-lactamic antibiotics

Carbapenems have a very broad spectrum of activity and represent a reliable choice for initial empirical treatment in the setting of critical illness.\(^{45}\)

Meropenem, an intravenously administered carbapenem, is commonly used in doses up to 2 g intermittently every 8 hours to treat severe infections caused by suspected or defined gram-negative infections, mostly Pseudomonas aeruginosa.\(^{45}\) Because it is not stable for more than ~4-6 hours at room temperature, meropenem has traditionally been considered an unacceptable choice for continuous IV infusion. However, investigators have shown that 24-hour stability can be maintained if the drug's temperature is kept below 4°C.\(^{46}\)

In order to evaluate the effectiveness of meropenem continuous infusion, Kuti et al. carried out a randomized study to determine the PK properties and stability of meropenem when administered to adults with cystic fibrosis by a continuous ambulatory drug-delivery infusion pump stored in a cold pouch between 2 freezer packs.\(^{47}\) Study participants were randomized to receive meropenem 125 mg/h or 250 mg/h (equivalent to 3 g and 6 g, respectively, over 24 hours) by continuous IV infusion for 12 hours. The study demonstrated that meropenem infusion rates of 125 mg/h and 250 mg/h provided serum drug concentrations greater than the minimum inhibitory concentration for pathogens considered meropenem-susceptible (\(\leq 4\) mg/L) and immediately resistant (8 mg/L), respectively.\(^{47}\)

Krueger et al.\(^{48}\) studied the pharmacokinetics of meropenem in two groups, each comprising eight healthy volunteers, who received the following doses: 500 mg as an intravenous infusion over 30 min three times a day (tid) versus a 250-mg loading dose followed by a 1 500 mg continuous infusion over 24 hours for group A and 1 000 mg as an intravenous infusion over 30 min tid versus a 500-mg loading dose followed by a 3 000-mg continuous infusion over 24 hours for group B. The high-dose continuous infusion had a robust probability of target attainment up to an MIC of 4 mg/L. The lower-dose probability of target attainment was still robust up to an MIC of 2 mg/L. Intermittent dosing was considered adequate against two common nosocomial pathogens,
Klebsiella pneumoniae and Enterobacter cloacae, based on the respective MICs as reported from the MYSTIC database; however, the high dose therapy administered as a continuous infusion was definitely more advantageous against Pseudomonas aeruginosa. The authors concluded that the continuous infusion mode of administration of meropenem should be provided in the empirical therapy of critically ill patients at risk for Pseudomonas aeruginosa infections.

In a recent study, Roberts et al. evaluated the plasma and subcutaneous tissue concentration-time profiles of meropenem administered by intermittent bolus dosing or continuous infusion to critically ill patients with sepsis and without renal dysfunction; they also used population pharmacokinetic modeling and Monte Carlo simulations to assess the cumulative fraction of response (CFR) against gram-negative pathogens likely to be encountered in critical care units. The authors randomized 10 patients with sepsis to receive equal doses of meropenem (3 g) either by intermittent bolus administration or by continuous infusion. Serial subcutaneous tissue concentrations were determined using microdialysis and compared with corresponding plasma data for first-dose and steady-state levels. Continuous infusion was more successful in achieving higher median trough concentrations in both plasma and subcutaneous tissue. According to the Monte Carlo simulation, intermittent bolus, extended and continuous infusion dosing methods were all successful in achieving 100% of pharmacodynamic targets against most gram-negative pathogens. However, regarding less susceptible pathogens as Pseudomonas aeruginosa and Acinetobacter species, extended or continuous infusions were superior.

In addition, Langgartner et al. reported on the PK parameters of meropenem in critically ill patients under continuous renal replacement therapy (CRRT). They found that appropriate antibacterial concentrations of meropenem in patients with CRRT are easily achievable with continuous infusion, thus representing an effective alternative dosing regimen to infusion bolus.

Likewise, Sakka et al. compared continuous and short-term infusions of imipenem-cilastatin in critically ill patients. Twenty patients with nosocomial pneumonia were randomized to receive either a loading dose of 1 g/1 g imipenem/cilastatin (as a short-term infusion) at time zero followed by 2 g/2 g imipenem-cilastatin per 24 hours as a continuous infusion for 3 days (N =10) or 1 g/1 g imipenem/cilastatin three times per day as a short-term infusion for 3 days (total daily dose, 3 g/3 g; N =10). The Monte Carlo simulation indicated that the probability of target attainment based on MIC values was robust for intermittent infusion (>80%) up to MICs of 1 to 2 mg/L. However, the corresponding value for continuous infusion was 2 to 4 mg/L, suggesting an advantage for this route of administration.

It is worthwhile to note that the administration of carbapenems in a continuous infusion can be challenging due to inherent stability issues. Therefore, the efficacy of prolonged carbapenem administration has been evaluated in a number of studies. Drusano developed a 2000-subject Monte Carlo simulation to evaluate the efficacy of different meropenem doses (0.5, 1 and 2 g, delivered every 8 hours) and different infusion times (0.5, 1, 2 and 3 hours) in attaining bactericidal exposure against 8096 isolates of P. aeruginosa with a range of MICs from 0.25 to 64 mg/L. This model demonstrated that a dose of 2000 mg delivered every 8 hours over a 3.2-hour infusion time would achieve a bactericidal exposure (40% T>MIC) in 96.7% of the subjects. Notably, for P. aeruginosa strains with a meropenem MIC of 16 mg/L, bactericidal exposure was achieved in over 80% of the simulated subjects.

Likewise, Kuti et al. employed Monte Carlo simulation to compare the rates of PD target attainment between various regimens of intermittent (30 min infusion) and prolonged (>3 hour infusion) meropenem infusion. They demonstrated that, regarding Enterobacteriaceae, the probability of attaining bacteriostatic (30% T>MIC) and bactericidal (50% T>MIC) exposures were high for both intermittent (0.5, 1 and 2 g every 8 hours) and prolonged (0.5, 1 and 2 g every 8 hours; 1 and 2 g every 12 hours) infusion regimens. Thus, for the same dose of meropenem (1 g every 8 hours), prolonging the infusion time from 30 minutes to 3 hours would increase bactericidal activity against Enterobacteriaceae only slightly, if at all (0% change for E. coli, Enterobacter cloacae and Serratia species and 0.5% change for Klebsiella pneumoniae and Enterobacter cloacae, based on the respective MICs as reported from the MYSTIC database; however, the high dose therapy administered as a continuous infusion was definitely more advantageous against Pseudomonas aeruginosa. The authors concluded that the continuous infusion mode of administration of meropenem should be provided in the empirical therapy of critically ill patients at risk for Pseudomonas aeruginosa infections.

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pneumoniae). However, against Acinetobacter and Pseudomonas species, the highest target attainment rates were achieved with a prolonged infusion regimen at a dosage of 2 g every 8 hours.54

The same issue was also addressed in a 2500-subject Monte Carlo simulation by Lomaestro and Drusano.55 In their model, three dosing regimens, a 1-hour infusion of 0.5 g of imipenem/cilastatin delivered every 6 hours, a 3-hour infusion of 0.5 g meropenem delivered every 8 hours and a 3-hour infusion of 1 g meropenem delivered every 8 hours were tested against strains of multiresistant susceptible S. aureus (M SSA), Klebsiella, Serratia, Enterobacter, Acinetobacter species and P. aeruginosa with MIC values for imipenem/cilastatin and meropenem ranging from 0.25 to 32 mg/L. All three dosing regimens were equally successful in effecting high rates of bactericidal exposure against M SSA and Enterobacteriaceae. However, against Acinetobacter species and P. aeruginosa, optimal bactericidal exposure was achieved with a 3-hour infusion of 1 g meropenem delivered every 8 hours.55

Furthermore, Kotapati et al.56 compared the clinical and economic outcomes of two meropenem intermittent (<30 min) infusion strategies of 0.5 g and 1 g delivered every 6 hours and 8 hours, respectively, against infections caused by various gram-positive and gram-negative pathogens. No significant differences in clinical and microbiological success rates, length of stay or adverse effects were observed between the two groups. In addition, the daily drug acquisition costs were significantly lower when meropenem was administered at a dose of 0.5 g every 6 hours. It should be mentioned that a minority of the treated patients sustained infections caused by P. aeruginosa strains. However, a subgroup analysis was not performed due to the small number of subjects.56

On the other hand, in a three-way crossover study by Jaruratanasirikul et al.,57 the pharmacodynamics of three different meropenem infusion regimens were evaluated in 9 patients with VAP caused by P. aeruginosa (MIC ranging from 0.125 mg/L to 6 mg/L) and Acinetobacter species (with a MIC of 4 mg/L). Patients were randomized to receive meropenem in three regimens consecutively, beginning with a bolus injection of 1 g every 8 hours for 24 hours, followed by a 3-hour infusion of 1 g every 8 hours and concluding with a 3-hour infusion of 2 g every 8 hours. In addition, T >MICs for MICs of 1, 4, 8, and 16 mg/L were calculated from the individually fitted concentration-time curves. This study showed that optimal bactericidal exposure against pathogens with an intermediate resistance (MIC of 16 mg/L) could only be achieved with a 3-hour infusion of 2000 mg of meropenem delivered every 8 hours.57

Piperacillin/tazobactam (P/T) is another beta-lactam antimicrobial widely used in the ICU. Notably, P/T solutions have previously been shown to be stable at 37°C for at least 24 hours.58

Tam et al.59 performed a retrospective analysis in order to evaluate the effectiveness of P/T monotherapy in cases of bacteremia due to P. aeruginosa with P/T MIC values at the highest end of susceptibility as defined by the Clinical Laboratory Standards Institute (32 mg/L and 64 mg/L). They conducted two parallel studies, the first of which included cases of bacteremia due to P. aeruginosa strains with MIC values 32 or 64 mg/L (N =7) and the second of which focused on isolates with MIC values <16 mg/L (N =10). Beta-lactams (carbapenems, cefepime, ceftazidime), quinolones and aminoglycosides were used as comparator drugs. An intermittent P/T infusion regimen was employed in all cases. This study demonstrated a significantly higher 30-day mortality in the subgroup with the higher MIC values (85.7% vs. 22.2%; P=0.004). Furthermore, an APACHE II score>15, a longer hospital stay before the first positive culture and P/T treatment were all factors significantly associated with a higher risk for 30-day mortality in the logistic regression analysis. Despite their disappointing findings, the authors asserted that P/T might be a reasonable treatment option for P. aeruginosa bacteremia, although alternative dosing regimens such as prolonged or continuous infusion might be considered in treating strains with high P/T MIC values.59

However, data on the clinical efficacy of piperacillin administered by continuous infusion are scant.60-64 In a study involving 40 septic critically ill patients, Rafati et al.60 demonstrated that, when the MIC was 16 mg/L, the target %T >MIC was achieved in all patients treated with continuous infusion (2 g over 0.5 h as a loading dose, then
8 g daily over 24 h) but only in 62% of those patients treated with intermittent infusion (3 g every 6 hours over 0.5 hours). Moreover, piperacillin continuous infusion was associated with a more rapid resolution of infection compared to intermittent infusion as demonstrated by APACHE II scores (P=0.04).60

In another study, Bulitta et al.64 reported PK/PD data for three different modes of piperacillin administration: short infusion (3 g in 30 min every 4 h), prolonged infusion (3 g in 4 hours every 8 hours) and continuous infusion (8 g in 24 hours) in 8 adult patients with cystic fibrosis. In the Monte Carlo simulation, they found that %T>M was 100% at MIC ≤16 mg/L for continuous infusion, while for intermittent infusion it varied from 55% to 100% depending on MIC values.64

A controlled study by Grant et al.61 involving 98 hospitalized patients with community or hospital-acquired infections reported on the clinical success rates of P/T continuous and intermittent infusion strategies. They found a non-significant higher success rate for the continuous infusion mode versus the intermittent one (94% vs. 82%; P=0.081), as well as a significantly lower number of days to fever resolution and lower costs for the continuous infusion group.61

Other studies, however, produced contrasting results. Li et al.62 randomized patients with complicated intra-abdominal infections caused by pathogens with a low a piperacillin/tazobactam MIC to receive either P/T by continuous infusion (13.5 g over 24 h) or intermittent infusion (3.375 g every 6 h). Based on data from 56 patients for whom the pharmacokinetic analysis was available, they concluded that the infusion method had no influence on PK parameters.62

A randomized study on 262 hospitalized patients with complicated intra-abdominal infections was performed by Lau et al.63 in order to compare piperacillin-tazobactam continuous infusion (12 g/1.5 g administered continuously over 24 h) with the standard intermittent infusion strategy (3 g/0.375 g administered over 30 min every 6 h). After analyzing 167 clinically evaluable patients, they noted that the rates of clinical cure or improvement at the test-of-cure visit for patients treated with continuous infusion or intermittent infusion were 86.4% and 88.4%, respectively (P=0.817). Additionally, bacteriological success and defervescence were similar between the two groups.63

Recently, Boselli et al.65 randomized 40 patients with microbiologically documented VAP to receive P/T in a continuous infusion at a daily dose of 12/1.5 g or 16/2 g. Serum and alveolar concentrations of piperacillin/tazobactam were recorded for the two groups. The authors reported that the percentage of epithelial lining fluid (ELF) penetration for the two dosing regimens was 40-50% and 65–85%, respectively. Both serum and alveolar P/T concentrations were correlated to the patients’ creatinine clearance, suggesting wide pharmacokinetic variability. They also noted that continuous P/T infusion at a dose of 12/1.5 g/day might lead to insufficient antibiotic ELF concentrations in patients with no/mild renal insufficiency suffering from VAP caused by pathogens with high P/T MIC values; they suggested that, in that case, a continuous P/T dose of at least 16/2 g/day might be more appropriate. In patients with moderate/advanced renal failure, both dosages (16/2 g and 12/1.5 g) achieved serum concentrations far above the 35-40 mg/L MIC threshold.65

Recently, Lorente et al.66 performed a retrospective study of 83 patients with VAP caused by gram-negative bacteria who received initial empirical antibiotic therapy with P/T. Thirty-seven patients were treated with continuous infusion while 46 were treated with intermittent infusion; no difference existed between the two groups in terms of demographic characteristics, severity scores, comorbidities or renal function. A significantly higher rate of clinical cure was noted for the patients treated with continuous infusion compared to those treated with intermittent infusion (33/37 [89.2%] vs. 26/46 [56.5%]; P=0.001). However, there were no significant differences in mortality rate and in the duration of mechanical ventilation or in the length of ICU stay. Notably, logistic regression analysis showed that the probability of VAP clinical cure was higher with the continuous infusion strategy when the culprit pathogen had a MIC at the higher value of susceptibility, i.e., 8 mg/L (P=0.049) or 16 mg/L (P=0.03).66

Piperacillin penetration into the tissue of critically ill patients with sepsis was evaluated in a prospective randomized study of 13 critically ill adult patients with known or suspected sepsis.67
Patients were randomized to receive piperacillin/tazobactam either via bolus administration (4 g/0.5 g every 6 or 8 hours) or via continuous administration (day 1: 4 g/0.5 g piperacillin–tazobactam bolus infusion followed immediately by a continuous 24-hour infusion of 8 g piperacillin/1 g tazobactam; day 2 and onward: 12 g/1.5 g piperacillin–tazobactam administered by 24-hour infusion). Patients treated with continuous administration had statistically significantly higher median plasma concentrations on day 2 compared to patients treated with bolus administration (16.6 vs. 4.9 mg/L; \(P=0.007\)), even though they were given a 25% lower piperacillin dose. Median tissue concentrations were not statistically different on day 1 and day 2 between the two groups. The authors concluded that the tissue pharmacodynamic targets were achieved more successfully with the continuous infusion regimen.67

The efficacy of an extended infusion dosing strategy for P/T in treating P. aeruginosa infections was explored in a retrospective study by Lodise et al.68 The authors employed Monte Carlo simulation to identify the optimal method of administering P/T for the treatment of P. aeruginosa infections. Their analysis revealed that the probability of attaining a 50% T>MIC (near bactericidal effect) was higher when P/T was administered in a 4-hour infusion at dose of 3.375 g every 8 hours compared to a 30-min infusion of 3.375 g every 4 to 6 hours. These two dosing regimens were validated in a cohort of 194 patients (65% of which were ICU patients), where 102 patients received the extended infusion regimen. All strains were susceptible to P/T, according to the Clinical Laboratory Standards Institute criteria (i.e., MIC≤64 mg/L). Classification and regression tree analysis revealed that an APACHE II score ≥17 was the most significant predictor of 14-day mortality. Overall, no statistically significant difference was observed between the two groups in terms of 14-day mortality and median length of hospital stay. However, when patients were stratified according to the severity of their illness, a significantly lower 14-day mortality (\(P=0.04\)) and median length of hospital stay (\(P=0.02\)) was evidenced for patients with APACHE II ≥17 who received the prolonged infusion regimen. The authors concluded that a P/T prolonged infusion regimen should be favored for the treatment of P. aeruginosa infections, particularly in critically ill patients.68

This study also highlighted the notion that critically ill patients are the most likely to benefit from strategies that optimize drug exposure and pharmacodynamics.

Therefore, the data favoring continuous/prolonged administration of antimicrobials with time-dependent patterns of killing in the intensive care unit are strong though not conclusive. Further studies should probably focus on critically ill patients with severe infections, a group most likely to benefit from this dosing regimen.30

Once daily (or extended interval) aminoglycoside regimens for critically ill patients

Aminoglycosides constitute one of the oldest classes of antimicrobial agents. Their activity follows a concentration-dependent pattern with a significant post-antibiotic effect.69 In the 1980s, Moore et al. advanced the use of Cmax/MIC as a marker of aminoglycoside efficacy; they proposed that a Cmax/MIC value of 10-12 is associated with a higher probability of treatment success.14, 15 Following this work, Kashuba et al. have shown that attainment of a Cmax/MIC ≥10 results in a faster clinical improvement of patients with pneumonia caused by gram-negative pathogens.70, 71 In addition, this strategy was shown to be associated with a lower probability of selecting resistant strains.72 These results strongly supported the rationale behind the once daily (or extended interval) dosing schedule for aminoglycosides. Several studies have suggested that this dosing regimen is as effective as intermittent dosing and carries a lower risk of toxicity.73 A weight-based nomogram using a once-daily dose of 7 mg/kg for gentamycin and tobramycin and allowing dose interval adjustments on the basis of a single subsequent plasma level assessment (obtained 6-14 hours following the start of aminoglycoside infusion) has been proposed by Nicolau et al.74 This dosing strategy was designed to maximize the efficacy of aminoglycosides against Pseudomonas aeruginosa and aims to achieve a peak concentration of 20 mg/L at one hour following drug administration, assuming a P. aeruginosa MIC <2 mg/L.74 The proposed nomogram became known as the “Hartford Hospital nomogram” and is very popular among others.
physicians treating ward patients with infections caused by gram-negative pathogens. H owever, the applicability of this dosing schedule in critically ill patients has been questioned. The main concerns include the increased volume of distribution of these patients, which may result in subtherapeutic drug concentrations, and the variability the patients exhibit in renal function, metabolic and hemodynamic state, which may influence drug clearance and elimination.

Sangha et al. studied the first-dose PK parameters of gentamycin delivered once daily to critically ill patients with open fractures at doses of 2 and 6 mg/kg. They found that the 6 mg/kg dose resulted in higher Cmax values but greater variability. The mean volume of distribution of the patients who received the 6 mg/kg dose was 0.4 L/kg.

A retrospective study by Finnel et al. evaluated the "Hartford" nomogram in trauma patients. They studied 49 patients with a creatinine clearance >40 mL/min/1.73 m² who were administered gentamycin or tobramycin once daily at a dose of 7 mg/kg and found that the "Hartford" nomogram correctly predicted the dosing interval in all but one patient (98%). In addition, the mean Vd for their patients was 0.28±0.09 L/kg, similar to the value reported in the study by Nicoalu et al. They concluded that the "Hartford" nomogram is applicable to this subset of patients.

Barletta et al. evaluated PK/PD parameters in a cohort of critically ill trauma patients treated with gentamycin or tobramycin once daily. The mean Vd of their patients was 0.3L/kg, with an intersubject variability of 33.8%. Four out of the 19 studied subjects experienced prolonged drug-free intervals (>12 hours). The investigators cautioned against the use of the "Hartford" nomogram in critically ill trauma patients and suggested individualized dosing based on at least two serum drug concentrations.

Furthermore, the PK/PD parameters of gentamycin and tobramycin given once daily at a dose of 7 mg/kg were investigated in a prospective study by Bujik et al. on medical and surgical ICU patients. As expected, they observed lower clearances and higher drug half-life times for patients with a reduced creatinine clearance (<60 mL/min). Importantly, they noted that in patients in shock, the Vd was significantly higher, elimination half-life was increased and Cmax values were lower compared to patients without shock. However, a Cmax/MIC value of 10 was achieved in the majority of the subjects. Finally, they noticed that the "Hartford" nomogram would have predicted the correct dose interval in only 62% of the patients. They concluded that although a dose of 7 mg/kg can achieve therapeutic targets in critically ill patients, drug concentration monitoring is nevertheless warranted.

Toschlog et al. also evaluated the applicability of the "Hartford" nomogram in critically ill trauma patients. In their study, 79 critically ill trauma patients were administered gentamycin or tobramycin at a dose of 7 mg/kg once daily and drug plasma levels were subsequently assessed at 10 hours. Out of the 79 treated patients, 46 (58%) had plasma drug concentrations lower than 2 mg/L at 10 hours. Thus, these patients were exposed to drug-free periods longer than the presumed aminoglycoside post-antibiotic effect. At univariate analysis, younger age, high creatinine clearance and lower resuscitation volumes (implying effective resuscitation and increased drug clearance) were the factors significantly associated with drug plasma concentrations lower than 2 mg/L at 10 hours.

A retrospective study on 102 medical ICU patients by Rea et al. also addressed this issue. The authors demonstrated that the chance of achieving a Cmax≥10 x MIC with a once-daily dosing at 7 mg/kg was 20% for gentamycin and 40% for tobramycin in their study population. In addition, as in previous studies, Vd and drug clearance exhibited significant variability.

Similar results were obtained from critically ill burn patients. A retrospective study by Conil et al. assessed amikacin PK/PD data in critically ill burn patients. Thirty-nine subjects received amikacin at a dose of 20 mg/kg once daily for the treatment of infected burn wounds. They noted that a Cmax/MIC ≥6 and 8 was attained only in 47% and 16% of the included patients, respectively. In addition, Cmax was negatively associated with the percentage of the burn surface (r=0.40; P<0.015) and the Unit Burn Standard (UBS) index (r=0.4; P<0.014). Thus, the average Cmax was significantly lower in patients with >15% burned area (45.95±9.19 mg/L vs 58.87±11.97 mg/L; P=0.003) and it was negatively correlated with the quantity of infused fluids during dosing (r=0.7; P=0.02). Furthermore, amikacin clearance was
positively associated with creatinine clearance ($r=0.51; P<0.0017$). Therefore, the average amikacin clearance was $178.18\pm70.56$ mL/min in patients with a creatinine clearance $>120$ mL/min and $123.49\pm46.47$ mL/min in patients with a creatinine clearance $<120$ mL/min ($P<0.009$). Moreover, $V_d$ was positively correlated with the UBS index ($r=0.36; P=0.02$). Based on their results, the authors suggested that higher doses of amikacin (25-30 mg/kg) should be considered for patients with burns $>15\%$ of total surface area and for patients whose creatinine clearance is $>120$ mL/min.85

Similarly, Bracco et al.86 employed extended-interval tobramycin dosing for the treatment of Pseudomonas species infections in a burn ICU. Twenty-three burn patients were treated with tobramycin at doses ranging from 80 to 350 mg, with dosing intervals between 16 and 36 hours. Assuming a MIC of 0.5 mg/L for tobramycin-sensitive pathogens, the investigators aimed to achieve a tobramycin $C_{max}$ of 8 mg/L. They observed that only 35% of the included patients eventually had peak serum tobramycin levels within the optimal range. In addition, a weak but significant correlation between creatinine and tobramycin clearance was observed. Furthermore, they noted that for a target tobramycin $C_{max}$ of 8 mg/L, a median optimal dose of 3.8 mg/kg (range 2.3-9.2 mg/kg) and a median administration interval of 36 hours (range 9.5-120 hours) would be required.86

For the time being, it seems prudent for physicians in the critical care setting to administer aminoglycosides in a single, reasonably high dose (e.g., at least 7 mg/kg for gentamicin), accounting for the increased $V_d$, in order to maximize efficacy; further treatment should be individualized on the basis of serial drug plasma level assessments. Additionally, small treatment periods (3-5 days) should be considered.87

**Dealing with the problem of emerging antimicrobial resistance: the paradigm of "MIC creep"**

In clinical practice, glycopeptides, notably vancomycin, represent the treatment of choice for severe infections caused by methicillin-resistant *Staphylococcus aureus*.31, 32 Despite the extensive use of vancomycin, only nine cases of vancomycin-resistant *S. aureus* (VRSA), defined by a vancomycin MIC of 16 mg/L or greater, have been identified to date. As of 2007, about 100 cases of vancomycin-intermediate *S. aureus* isolates (VISA), defined by a vancomycin MIC of 4-8 mg/L, have been reported worldwide.88 However, the emergence of glycopeptide-resistant enterococci has prompted authorities to advocate susceptibility testing for all *S. aureus* strains.89 In 2006, the Clinical and Laboratory Standards Institute lowered the *S. aureus* vancomycin susceptibility and resistance breakpoints from 4 to 2 mg/L and from 32 to 16 mg/L, respectively.90

Nevertheless, the clinical and bacteriological failure of vancomycin in the treatment of staphylococcal infections does occur. Cosgrove et al.91 reviewed 31 cohort studies (involving almost 4,000 patients) that provided mortality data for patients with *Staphylococcus aureus* bacteremia (36% caused by MRSA). They found that MRSA bacteremia was associated with a higher mortality compared to methicillin-susceptible *S. aureus* (MSSA) bacteremia, with an OR of 1.93 (95% CI: 1.54-2.42; $P<0.001$). This difference persisted in a subgroup analysis of 11 studies that provided adjustments for the severity of illness (OR: 1.88, 95% CI: 1.33-2.69; $P<0.001$ (91). More recently, a meta-analysis by Athanassa et al. also reported on the impact of methicillin resistance on the mortality of patients with VAP caused by *S. aureus*.92 Based on 8 studies that provided relevant data, they have demonstrated that crude in-hospital mortality is higher for MRSA VAP as opposed to MSSA VAP (OR 1.79 95% CI 1.210-2.65); this was also the case for crude ICU mortality (OR 2.49, 95% CI 1.54-4.06, data derived from 3 studies). Furthermore, in 4 of the studies included in this review, mortality was adjusted for potential confounders. After adjustment, 3 out of these 4 studies failed to demonstrate any difference in mortality between MRSA and MSSA VAP.92

Furthermore, the relevance of the MIC values in guiding treatment choices for MRSA infections has been called into question. Indeed, treatment failures are not uncommon, even when the MRSA strains are conventionally considered susceptible to vancomycin (i.e., MIC $\leq$ 2 mg/L).93, 94 In addition, a number of observational studies have suggested
that vancomycin treatment failure is more likely in cases of MRSA strains with a MIC at the higher limits of “susceptibility” (1-2 mg/L), a phenomenon aptly called “MIC creep”.95-97 Following these reports, Steinkraus et al.98 investigated trends in vancomycin MIC values for MRSA over a period of 5 years (2001-2005) by employing Etest and geometric mean MIC values. They demonstrated a 1.5-fold increase in the vancomycin geometric mean MIC values over the study period. Furthermore, they noted that the percentage of MRSA strains with a vancomycin MIC ≤0.5 mg/L had decreased from 46% in 2001 to 5% in 2005, while the percentage of isolates with a vancomycin MIC >1mg/L had increased from 0 to 7%.96 In another study, Wang et al.99 noted that the percentage of S. aureus isolates (MRSA and MSSA) with a vancomycin MIC value of 1 mg/L had significantly increased from 20 to 70% over a 5-year study period; this change was more noticeable for MSSA strains.99

Recently, the relationship between the clinical outcome of Staphylococcus aureus bacteremia and the MIC of vancomycin was clearly demonstrated in a prospective clinical study by Soriano et al.100 The authors observed that among 168 patients treated with vancomycin for S. aureus bacteremia, a MIC for vancomycin >2.0 mg/L was independently associated with a significantly greater risk of death at 30 days compared with an MIC value of 1.0 mg/L (O R: 6.39, 95% CI, 1.68-24.3; P<0.001).100 Heteroresistance, defined as the presence of various susceptibilities to an agent within a microbial population,101 has been considered a potential explanation for these findings.100

The “MIC creep” phenomenon is probably related to vancomycin underdosing (due to fears of toxicity) in combination with poor tissue penetration.102 The importance of the last factor should be underscored.41 In a study on mechanically ventilated patients, Lamer et al.103 showed that the blood-to-alveolar lining fluid (ALF) vancomycin ratio was 6:1; in this study, vancomycin concentrations in the ALF ranged from 0.4 to 8.1 mg/L.103 Moreover, a multicenter study demonstrated that treatment failure for cases of VAP caused by MRSA was more likely for patients treated with vancomycin administered in intermittent doses compared to linezolid.104

The accumulated evidence suggests that our strategies for managing severe staphylococcal infections should be revisited. First, precise tests for the determination of MIC, such as the Etest or broth microdilution, should be considered in settings with a high incidence of MRSA infection;102 tests for heteroresistance should also become widely available and standardized.105 In addition, the treatment schedule should take into account both the in vitro bacterial susceptibility and the PD behavior of the agent itself.11 For instance, continuous vancomycin infusion (preceded by a loading dose) has been shown to reliably achieve an effective concentration of the antimicrobial agent at the infection site.41, 107 Rello et al. observed a lower mortality in patients with MRSA VAP who received continuous vancomycin infusion.108 Thus, it has been recently suggested that for a pathogen with an MIC of 1 mg/L, the minimum trough concentration of vancomycin would have to be ≥15 mg/L to generate an AUC/MIC of 400.109

However, increasing vancomycin doses to achieve the target trough level in cases with higher vancomycin MIC values may not improve long-term outcomes.37 Under these circumstances, alternative antimicrobial agents, as linezolid110, 111 and daptomycin,112, 113 should be strongly considered. Therefore, in settings where there is a high prevalence of MRSA strains with a vancomycin MIC ≥1 mg/L, initial therapy should incorporate alternative antimicrobial agents, such as linezolid in the case of pneumonia. De-escalation to vancomycin, along with therapeutic drug monitoring, should be performed if a MRSA strain with a lower vancomycin MIC is isolated. From this point of view, the “MIC creep” phenomenon represents an excellent paradigm for how the correct use of older agents and the inclusion of newer agents into de-escalation practices might be employed in the treatment of infections due to emerging resistant pathogens.

Conclusions

Critical illness may influence antibiotic PK parameters in a variety of ways. To increase the likelihood of success, modern antimicrobial treatments in the critical care setting should take into account the special PD characteristics of each of the
administered agents, employ therapeutic drug monitoring and consider pathogen susceptibility patterns.

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