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Pharmacokinetic/pharmacodynamic (PK/PD) considerations in the management of Gram-positive bacteraemia

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Abstract

Bloodstream infections are among the most serious infections of hospitalized patients and are associated with high mortality, especially among those with severe sepsis and septic shock. A range of organ dysfunctions, together with drug interactions and other therapeutic interventions (e.g. haemodynamically active drugs and continuous renal replacement therapies) may have a strong impact on antimicrobial drug pharmacokinetics in critically ill patients. Intrinsic pharmacokinetic (PK) and pharmacodynamic (PD) properties are the major determinants of the in vivo efficacy of antimicrobial agents. Knowledge of PK/PD parameters is essential in facilitating the translation of microbiological activity into clinical situations and ensuring a successful outcome. This review analyses the typical patterns of antimicrobial activity of classes of agent commonly utilized against Gram-positive pathogens in hospital settings, and their corresponding PK/PD parameters, focusing on the PK/PD dosing approach.

Keywords:

Bloodstream infections

Antimicrobial agents

Pharmacokinetics

Pharmacodynamics

1. Introduction

Bloodstream infections are among the most serious infections of hospitalized patients and are associated with high mortality, especially among those with severe sepsis and septic shock [1–4]. Some studies have demonstrated an important relationship between hospital mortality and inadequate empirical antimicrobial treatment of bacteraemia (Fig. 1.). It is not surprising that appropriate therapy is related to lower mortality, but what is surprising is that appropriate therapy is related to mortality ranging from 30% to 50%, depending from the study.

[Fig. 1. here]

What does the term ‘appropriate therapy’ mean? It is usually defined as either the presence of antimicrobial agents directed against a specific class of microorganisms, or the administration of drugs to which the microorganism responsible for the infection is susceptible [5]. These definitions, in the mind of many clinicians, represent only the minimum, an appropriate dosing regimen also including early administration and the correct drug dose or schedule of administration. Despite appropriate dosing regimens, failure of antimicrobial therapy may occur due to impaired immunological function or the inability of the antimicrobial to achieve adequate concentrations at the infection site due to alterations in its pharmacokinetics resulting from underlying pathophysiological conditions.

In the last decade it has become apparent that the intrinsic pharmacokinetic (PK) and pharmacodynamic (PD) properties of antimicrobial agents are the major determinants of their in vivo efficacy and knowledge of them enables the use of optimal dosing regimens and the determination of clinically relevant susceptibility breakpoints [6]. In this paper

the use of PK/PD relationships is discussed, with a special focus on agents against Gram-positive organisms.

2. Pharmacodynamic measures of antimicrobial effects

Antimicrobial pharmacodynamics is the discipline that attempts to link measures of drug exposure to their microbiological or clinical effects [7]. Only the free or unbound fraction of a drug is available for antimicrobial activity [8], which must be considered when examining the relationship between PK/PD parameters and in vivo activity [9]. A large number of studies have defined the PK/PD properties of the major classes of antibiotic, and have observed three patterns of activity [10,11]. The first is characterized by concentration-dependent killing and a prolonged post-antibiotic effect (PAE). Higher drug concentrations result in more rapid and extensive organism killing, and the peak/MIC (C_{max}/MIC) and/or the area under the concentration–time curve at 24 h/MIC (AUC_{0-24}/MIC) ratios are the best PK/PD parameters correlating with treatment efficacy. Dosing of drugs exhibiting this pattern of activity is optimized by the administration of large doses. Furthermore, a prolonged PAE allows the lengthening of dosing intervals (e.g. a once-daily dose regimen). This pattern is predictive of the activity of aminoglycosides, fluoroquinolones, metronidazole and daptomycin.

The second pattern is characterized by time-dependent killing and a minimal to moderate PAE. Extending the duration of exposure optimizes the antimicrobial activity. The time that free antimicrobial concentrations remain above the MIC ($T_{>MIC}$) for the organism is the PK/PD index that correlates with bacterial killing and microbiological response. The shorter the drug elimination half-life, the more frequent the dose fractioning must be. In some circumstances the use of a continuous intravenous

infusion, which maintains the $T_{>MIC}$ at 100%, may be the most effective way of maximizing pharmacodynamic exposure, especially if higher $T_{>MIC}$ are required [12].

The different classes of β -lactam (penicillins, cephalosporins, monobactams and carbapenems) exhibit this pattern of activity.

Concentration-independent killing and prolonged PAE characterize the final pattern of activity. Higher drug concentrations at most only slightly enhance organism killing, but produce prolonged suppression of organism regrowth. The goal of dosing is to optimize the amount of drug, and the AUC_{0-24}/MIC ratio is the index most closely associated with efficacy. This is the pattern observed for glycopeptides, linezolid, quinupristin–dalfopristin, tetracyclines, clindamycin, azithromycin and the glycylcyclines.

A strong interrelationship (so-called colinearity) exists among the PK/PD indexes. With each increase in dose level, C_{max} , AUC_{0-24} and $T_{>MIC}$ will rise. Regarding the emergence of resistance, an increasing amount of data from in vitro and animal infection models have demonstrated a strict relationship between the magnitude of PK/PD parameters and the prevention of resistance, although data in humans are more limited [13].

3. Critical illness and pharmacokinetic changes

Critically ill patients with bloodstream infections include representatives of all age groups who have a range of organ dysfunctions related to severe acute illness that may complicate long-term illness. These factors, together with drug interactions and other therapeutic interventions (e.g. haemodynamically active drugs and continuous renal replacement therapies), may affect drug pharmacokinetics [14,15].

Variations in the extracellular fluid content and/or in renal or liver function are the most relevant and frequent pathophysiological mechanisms possibly affecting drug disposition in critically ill patients. Hydrophilic antimicrobials (e.g. β -lactams, aminoglycosides and glycopeptides) and renally excreted, moderately lipophilic antimicrobials (e.g. ciprofloxacin, gatifloxacin and levofloxacin) have to be considered at high risk of presenting substantial daily fluctuations in plasma concentration that may require repeated dosage adjustments. Hydrophilic antimicrobials exhibit a volume of distribution (V_d) limited by the extracellular space, and their plasma and interstitial concentrations may drop dramatically because of substantial fluid extravasation to the interstitial space, known as third spacing. On the other hand, for lipophilic antimicrobials presenting larger V_d , the dilution of interstitial fluids is less relevant [16].

Several pathophysiological conditions may cause an increase of V_d and dilution of antimicrobials in plasma and extracellular fluids so that an increase in dosage should be considered [16]. This may be especially true for hydrophilic concentration-dependent antimicrobials with a small V_d (mainly aminoglycosides), which require loading doses at the start of therapy. The presence of an oedematous status, regardless of the underlying pathogenetic mechanism, plays a major role in altering the distribution of antimicrobials. Sepsis and trauma are the most common among the several causes of oedema. Higher dosages for most hydrophilic antimicrobials (either aminoglycosides or β -lactams) should therefore be considered to ensure therapeutic concentrations are maintained. Abundant intravenous fluid therapies, total parenteral nutrition, pleural effusion, mediastinitis, peritoneal exudates and ascites, by causing an increase in the extracellular compartment fluid, may lead to a significant increase in V_d and the

resulting dilution may justify higher dosages. In surgical patients, indwelling drainages may represent a pathway of antimicrobial loss and contribute to lower antimicrobial levels. Hypoalbuminaemia, a common condition in critically ill patients, may contribute to fluid extravasation and antimicrobial dilution by reducing plasma oncotic pressure, whereas the increase in the free fraction of drugs may increase their V_d . With reference to renally excreted highly albumin-bound antimicrobials (e.g. teicoplanin and ceftriaxone), the increase in free fraction caused by hypoalbuminaemia may promote not only more extensive distribution but also higher renal clearance.

In the intensive care unit (ICU) setting the use of haemodynamically active drugs (e.g. dopamine, dobutamine and furosemide) can modify renal blood flow and thereby glomerular filtration, tubular secretion rates and renal clearance. Extensive third-degree burns (>30–40% body surface) cause enhanced renal clearance, with more relevant pathophysiological changes occurring beyond 48 h, when the hypermetabolic phase usually begins. This period is frequently characterized by an increase in cardiac output leading to enhanced renal blood flow and, in turn, glomerular filtration rate, which may become significantly increased [17,18]. As a consequence, the renal clearance of most hydrophilic and moderately lipophilic antimicrobials is expected to increase significantly during the hypermetabolic phase. The same applies to the early phase of sepsis, which may cause an increase in cardiac output and renal blood flow [19]. Renal failure is also a common condition in the ICU setting.

Therapeutic drug monitoring may be of great value in all the clinical conditions described above, helping to optimize drug exposure in the individual patient. Several

clinical trials have demonstrated its positive impact on clinical outcome and the cost of hospitalization [20].

4. Glycopeptides

The study of the pharmacodynamics of glycopeptides in animal models supports the concept that sustained higher concentrations or more frequent dosing can improve survival in animal models of infective endocarditis [21,22]. $T_{>MIC}$ was thus initially considered the most important PK/PD marker for efficacy. However, in a *Streptococcus pneumoniae* non-neutropenic mouse peritonitis model, Knudsen et al. demonstrated that both $T_{>MIC}$ and C_{max} are of major importance for predicting the effect of single-dose glycopeptide treatment [23]. The same authors subsequently evaluated the effect of a wide spectrum of different treatment regimens with vancomycin and teicoplanin in an immunocompetent mouse peritonitis model with *Staphylococcus aureus* and *S. pneumoniae* as infective organisms [24]. The data showed that $C_{max-free}$ was of major importance in the one- and two-dose trials, but this parameter alone could not explain the effects achieved in the multidose trials. In this setting, only $C_{max-free}$ in combination with AUC/MIC for vancomycin or $T_{>MIC-free}$ for teicoplanin was able to explain survival. In a subsequent review, Craig emphasized the role of AUC/MIC as predictive of efficacy not only for vancomycin but also for teicoplanin [11].

Several studies have emphasized the role of the AUC/MIC ratio as predictive of treatment efficacy. Hyatt et al. demonstrated that those patients treated with vancomycin monotherapy for enterococcal infections who achieved AUC_{0-24}/MIC values <125 had a higher probability of clinical failure and selection of vancomycin-resistant *Enterococcus faecium* [25]. In a population of elderly hospitalized patients with lower

respiratory tract infections caused by *S. aureus* and treated with vancomycin, Moise-Broder et al. showed that AUC_{0-24}/MIC values predicted clinical and bacteriological outcomes, with higher clinical success rates in the subset of patients with AUC_{0-24}/MIC values >350 (or approximately 400 for bacterial eradication) [26]. All patients in this study (both successes and failures) had $T_{>MIC} = 100\%$, establishing that vancomycin $T_{>MIC}$ at the 100% target is not predictive of outcome.

In critically ill patients, the pharmacokinetics of vancomycin, like other antimicrobials, shows broad variability and a significant change in both clearance and the distribution volume [27]. Higher doses of vancomycin seem to be necessary in the ICU, even when the pathogens have MIC values typical of susceptible microorganisms, and therapeutic drug monitoring is strongly recommended, with the aim of optimizing drug exposure in the individual patient. In a recent retrospective study by Del Mar Fernández de Gatta Garcia et al., higher distribution volumes (nearly twice the quoted value of 0.72 L/kg) and different vancomycin clearance–creatinine clearance relationships were found in ICU patients [28]. Renal function, the APACHE score (Acute Physiology and Chronic Health Evaluation), age and serum albumin accounted for more than 65% of vancomycin clearance variability. According to PK/PD analysis, vancomycin standard dosages led to a 33% risk of not achieving the recommended AUC_{0-24}/MIC breakpoint for *S. aureus*, possibly leading to an unfavourable clinical outcome. The results of Monte Carlo simulation revealed that doses of 3000 mg or even 4000 mg daily may be necessary to reach the highest probability of efficacy when susceptible *S. aureus* strains are involved in the infectious process; similar results were found for other *Staphylococcus* isolates. Regarding glycopeptide-intermediate *S. aureus* (GISA) strains,

doses as high as 5000 mg/day led to a maximum probability of a positive clinical outcome of only 80% for a value of 400 as the breakpoint. The results also point to the suitability of considering antimicrobial agents other than vancomycin when GISA strains are involved, as suggested by other authors [29].

With the aim of improving the results of vancomycin therapy, a variety of strategies such as higher doses, combination therapy and continuous infusion have been proposed. Continuous infusion might make treatment monitoring and adjustment easier and cheaper because vancomycin concentrations in serum are less variable and more sustained [30]. In a prospective multicenter randomized trial comparing critically ill patients with severe methicillin-resistant staphylococcal infections, continuous infusion of vancomycin resulted in therapeutic concentrations being achieved more quickly, less AUC variability between patients, fewer samples required to monitor treatment, and reduced 10-day antibiotic cost; clinical efficacy and safety were comparable to the intermittent infusion schedule [31]. AUC_{0-24}/MIC values were not investigated in this study, meaning that no adjustment was made for organisms having different MIC values. Given the variation in AUC_{0-24}/MIC that would result from the fourfold range in MIC values found in these patients (0.5–2.0 mg/L), it is not surprising that the AUC_{0-24}/MIC did not correlate with outcome, since dosage adjustments to target serum concentrations should make AUC_{0-24}/MIC values similar in all patients (successes and failures) [26]. Di Filippo et al. observed more favourable clinical outcomes in patients with continuous infusion of vancomycin in terms of improved organ function and leukocyte response, but overall disease evolution was not altered [32], probably because the study sample was too small ($N = 25$). Data suggesting improved clinical

cure and resolution of illness with continuous infusion of vancomycin in ICU patients are scarce. Nevertheless, a recent study by Rello et al. reported for the first time lower mortality rates among ICU patients with ventilator-associated pneumonia caused by oxacillin-resistant *S. aureus* receiving vancomycin in continuous infusion (25% vs. 55%) [33]. However, only a minority of the patients received continuous infusion of vancomycin ($N = 16$) and no detailed information on patients treated with continuous versus intermittent infusion was reported.

Finally, other authors have suggested that as vancomycin has a long elimination half-life (compared with β -lactams) and a prolonged Gram-positive antimicrobial effect, continuous infusion is unnecessary for most patients [34]. Larger and well-designed randomized trials are needed to clarify the clinical efficacy of this type of approach. The evidence to support advantages is very limited, as recently reported by the Infectious Diseases Society of America [35].

5. Linezolid, quinupristin–dalfopristin, daptomycin and tigecycline

5.1. Linezolid

This is the first member of a new class of antibacterial agents, the oxazolidinones, which act by inhibiting the formation of bacterial protein synthesis initiation complex, possibly by distorting the binding site for initiator tRNA [36]. It is a valid therapeutic alternative to glycopeptides against multiresistant Gram-positive strains such as staphylococci, streptococci and enterococci, which are particularly frequent in the ICU [37]. Linezolid is a time-dependent antimicrobial agent with a persistent antibiotic effect and the PK/PD indices $T_{>MIC}$ and AUC/MIC are important determinants of its efficacy in vitro and in vivo [38,39]. In several animal infection models, a $T_{>MIC} >40\%$ significantly

enhanced bacterial killing of pneumococci, and AUC/MIC ratios of 48–147 were necessary for a bacteriostatic effect [38,38,40]. Linezolid serum levels with $T_{>MIC} >50\%$ for pathogens with MICs of 2–4 mg/L can be obtained in healthy volunteers by administration of 600 mg every 12 h [41].

In critically ill patients Rayner et al. confirmed that both $T_{>MIC}$ and AUC/MIC are highly correlated with the probability of eradication and clinical cure within specific infection sites [38]. Higher success rates for linezolid may occur at AUC/MIC values of 80–120 for bacteraemia, lower respiratory tract infection and skin and skin structure infection. Chances of success in bacteraemia, lower respiratory tract infection and skin structure infection also appear to be higher when $T_{>MIC} >85\%$. However, as mentioned above, alterations in pharmacokinetic parameters (especially volume of distribution and clearance) are common in critically ill patients and suboptimal serum and tissue concentrations may be achieved when drugs are administered at the standard dosage, with the risk of therapeutic failure and development of resistance.

Buerger et al. have recently demonstrated a high inter-individual variability in linezolid interstitial concentrations in patients with sepsis or septic shock, suggesting that a more frequent linezolid daily dosing scheme would be more appropriate in this subpopulation of patients [42]. In order to optimize the time-dependence of linezolid, the administration by continuous infusion has been proposed. In an in vivo model of endocarditis, Jacqueline et al. showed not only that continuous infusion was more effective than intermittent doses, but also that switching from intermittent dosing to continuous infusion (at the same daily dose) led to in vivo bactericidal activity [43]. Moreover, a recent trial by Adembri et al. compared the pharmacokinetic/ pharmacodynamic profile of linezolid

administered by intermittent or continuous infusion in 16 critically ill septic patients [37]. In the intermittent infusion group, linezolid trough serum levels ($C_{\min}$) varied widely and were below the susceptibility breakpoint (4 mg/L) during the study period; in 50% of patients $C_{\min}$ was <1 mg/L. In the continuous infusion group, mean linezolid serum levels were more stable and, starting from 6 h, were significantly higher than $C_{\min}$ levels observed in the intermittent infusion group and were always above the susceptibility breakpoint. Moreover, $T_{>MIC} > 85\%$ for the free drug was more frequent in the continuous infusion group. Finally, with continuous infusion it was possible to achieve AUC/MIC values of 80–120 more frequently than with intermittent infusion. No differences in clinical efficacy or microbiological eradication between the two regimens were observed, probably because of the small number of subjects, and no specific side effects due to continuous infusion were noted.

Since constant exposure of bacteria to linezolid levels just above the MIC has been shown to play a role in the development of in vitro resistance [44], another potential advantage of continuous infusion is that, by maintaining adequate serum levels, it may also reduce the phenomenon of resistance and may increase safety. Further studies with a larger number of patients are necessary to demonstrate the possible clinical benefit and safety of this administration modality.

5.2. *Quinupristin–dalfopristin*

This is a 30:70 mixture of two naturally occurring water-soluble streptogramin antimicrobials – pristinamycin IA (quinupristin: RP 57669), a peptidic macrolactone, and pristinamycin IIA (dalfopristin: RP 54476), a polyunsaturated macrolactone [45]. They demonstrate synergistic activity against a wide variety of Gram-positive organisms,

including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *E. faecium* [46–48]. Activity against most strains of *Enterococcus faecalis* is lacking [49]. Individually the antibiotics are bacteriostatic but, in combination, bactericidal activity can be observed against staphylococci and streptococci, although not against *E. faecium* [50]. In vitro studies suggest that quinupristin–dalfopristin exhibits time-dependent killing but produces prolonged persistent effects against Gram-positive bacteria at concentrations above the MIC [48], allowing extended administration intervals of 8 h, despite the short half-lives of the two compounds (<1 h).

There are relatively few data to define the PK/PD parameter that predicts activity for quinupristin–dalfopristin. In vivo data using the neutropenic thigh model against *S. aureus* and *S. pneumoniae* showed AUC_{0-24}/MIC to be the best predictor of response [51]. Other investigators have suggested that minimum bactericidal concentration may be a more appropriate denominator for pharmacodynamic outcomes [52–53]. Due to the multiple active components of pharmacokinetic models, the appropriate PK/PD handling of quinupristin–dalfopristin is not easy. The observation that bioassay results may approximate the additive activity of each parent compound with its active metabolites has led to the suggestion of combining the pharmacokinetic parameters of all high performance liquid chromatography-measured compounds.

Adding the reported AUCs of all known active components (quinupristin, dalfopristin, cysteine–quinupristin, glutathione–quinupristin and pristinamycin IIA) from the selective bioassays produces a combined steady-state AUC over the administration interval of approximately 16–17 mg • h/L [54]. This corresponds to a total drug by AUC_{24} of approximately 34 mg • h/L and 50 mg • h/L for the 7.5 mg/kg every 12 h and 7.5 mg/kg

every 8 h regimens, respectively. For sensitive pathogens with a MIC of 1 mg/L, a 24 h total drug AUC/MIC ratio of 34–50 would be obtained. The effect of protein binding on these parameters may further reduce these ratios, as only free drug is active. However, since the difference in protein binding (55–78% for quinupristin and 11–26% for dalbapristin) of the two compounds is consistent, the magnitude of the PK/PD parameters based on free drug is not applicable for clinical use.

Thus, although AUC/MIC has been suggested as a marker for efficacy of quinupristin–dalbapristin, the most clinically effective value of this ratio has not been identified and human studies correlating PK/PD parameters with clinical outcomes are lacking [55].

5.3. Daptomycin

Daptomycin is a cyclic lipopeptide antimicrobial agent that only has activity against Gram-positive organisms. It is principally used to treat vancomycin-resistant enterococci, MRSA and glycopeptide-intermediate and -resistant *S. aureus*. [56]. It has been approved for the treatment of skin and soft tissue infections and *S. aureus* bloodstream infections, including right-sided endocarditis [57,58]. It was not successful in trials of community-acquired pneumonia and it has subsequently been shown that daptomycin is inactivated by surfactant, rendering it unable to kill bacteria in the alveoli [59,60].

Daptomycin has a unique mechanism of action; it binds to bacterial membranes and causes rapid depolarization of membrane potential, resulting in inhibition of protein, DNA and RNA synthesis, leading to bacterial cell death [61]. It is characterized by rapid concentration-dependent killing and a prolonged antibiotic effect against *S. aureus* and enterococci [62,63]. In murine neutropenic thigh models of *S. aureus* methicillin-

susceptible [64] or meticillin-resistant strains [65] infection, the AUC/MIC ratio has been correlated with outcome. In another neutropenic murine thigh infection model, Safdar et al. demonstrated that both the AUC/MIC_{0–24} ratio and the C_{max}/MIC ratio were strong predictors of in vivo efficacy [66]. In vitro pharmacodynamic studies have shown that a range of free AUC/MIC ratios (16.5–189) was associated with 80% maximum effect for various *Staphylococcus* and *Enterococcus* spp. [67]. In general, however, lower AUC/MIC exposures are required to achieve static or 80% maximum effects for enterococci compared with staphylococci [68]. Over a 24 h period, free daptomycin concentrations averaging 1–2 times the MIC are needed for a bacteriostatic effect and 2–4 times the MIC for >99% killing [69,70].

Due to daptomycin's concentration dependence, a once-daily dosing regimen has been proposed to optimize its pharmacodynamic properties and has demonstrated an improved safety profile compared with that of the initially evaluated twice-daily regimen [71–75]. A Monte Carlo prediction model analysis was conducted to determine if AUC/MIC targets could be achieved in a clinical setting [74]. An AUC/MIC ratio of 189 for the free drug generated maximum-kill ED₈₀ (the effective doses required to achieve 80% kill) against MRSA and *E. faecium* isolates tested. The Monte Carlo simulations predicted the probability of achieving a free drug AUC/MIC ratio of 189 to be 80.4%, 91.06% and 95.64% for doses of 4, 6 and 8 mg/kg once per day.

Cha et al. used an in vitro pharmacodynamic model with simulated endocardial vegetations incorporating protein to simulate regimens of daptomycin at 6 and 8 mg/kg/day and vancomycin at 1 g every 12 h against meticillin-resistant *S. aureus* and *Staphylococcus epidermidis*, glycopeptide-intermediate *S. aureus* and *S. epidermidis*,

and vancomycin-resistant *E. faecium* [75]. Both daptomycin regimens achieved greater than 99.9% kill by 8 h and demonstrated greater bacterial reduction than vancomycin against all tested isolates at 24, 48 and 72 h. Higher daptomycin dosage (i.e. 6 mg/kg intravenously once per day) is currently approved by the US Food and Drug Administration for *S. aureus* bloodstream infections, including patients with right-sided endocarditis [76].

At present there are no pharmacokinetic studies in ICU patients. Therefore monitoring of the drug for efficacy and for safety is recommended in these patients.

5.4. Tigecycline

This derivative of minocycline is the first of a new class of antimicrobials known as glycylcyclines. Tigecycline not only has in vitro activity against MRSA and vancomycin-resistant *E. faecium*, but also common Gram-negative aerobes, atypical pathogens and anaerobic pathogens, with the exception of *Pseudomonas aeruginosa* and *Proteus* spp. [77–81]. As with other tetracycline derivatives, tigecycline binds to the 30S ribosomal subunit, inhibiting protein synthesis and bacterial growth. The presence of a modified side chain on tigecycline, with respect to minocycline, circumvents resistance mechanisms that plague tetracycline and other antibiotics in this class. Tigecycline has been evaluated for the treatment of complicated skin and skin structure infections, complicated intra-abdominal infections, and pneumonia [82–83]. In vitro, tigecycline is characterized by time-dependent activity against *S. pneumoniae*, *Haemophilus influenzae*, and *Neisseria gonorrhoeae* [84–86]. Due to its prolonged PAE and relatively long half-life (approximately 40 h), tigecycline's AUC/MIC ratio is the PK/PD index most likely to be predictive of its clinical and microbiological efficacy [87–90]. In a *S. aureus*

neutropenic mouse thigh infection model, values of 15–20 for AUC_{0-24}/MIC were associated with stasis to a 90% reduction in bacterial burden [89]. Recent studies by Meagher et al. involved hospitalized patients with complicated skin and soft tissue infections enrolled in clinical trials and treated with tigecycline [91]. Multivariate logistic regression analyses identified AUC_{0-24}/MIC as being predictive of microbiological response to therapy. When considering *S. aureus* and/or group A streptococcal infections, $AUC_{0-24}:MIC$ values >17.9 were associated with 100% of patients having a microbiological success, whereas patients with $AUC_{0-24}:MIC$ values <17.9 had only a 50% response; a similar exposure–response relationship was also observed for clinical outcome. The breakpoints identified above reflect those obtained in patients with complicated skin and skin structure infections and should not be extrapolated to other infections [91–93]. The relationship between tigecycline exposure and response has also been evaluated in patients with complicated intra-abdominal infections [92]. Ninety-four percent of patients with an AUC/MIC ratio >6.96 had resolution of signs and symptoms of infection and required no further antimicrobial therapy. Compared with those with an $AUC:MIC$ ratio ≤ 6.96 , these patients were 5.7 times more likely to have a clinical response and 10 times more likely to have a microbiological response. Further studies are needed to determine whether the AUC/MIC ratio is a reliable pharmacodynamic parameter for predicting the outcome in patients receiving tigecycline.

6. Conclusion

Patients in ICUs are at high risk of developing bacterial infections with a high mortality rate. Every effort should be undertaken to minimize the rate of nosocomial infection by

appropriate infection control programmes, and the microbiological laboratory should be able to provide regularly updated reviews of resistance patterns for the most important pathogens isolated in the ICU [94]. Optimization of antimicrobial therapy is mandatory [95,96].

The aim of anti-infective therapy is to administer a dose of drug that will have an acceptably high probability of attaining the desired therapeutic effect while having an acceptably low probability of concentration-related toxicity. PK/PD relationships are the major determinants of in the vivo efficacy of antimicrobial agents and allow optimization of the dosage regimen to improve the outcome and reduce the selection of resistant mutants. Although there are relatively few clinical studies available in the ICU setting to deliver the proof of concept, several in vitro data and animal studies provide good evidence for the beneficial role of optimizing the PK/PD relationship for most of the antibiotics used in clinical practice. The MIC of an antimicrobial agent against the infecting pathogen is a very important parameter in this relationship and it is the responsibility of the microbiology laboratory to deliver a qualified and quality-assured estimate of this value; the clinician may then consider this information when choosing the correct antimicrobial treatment. In the ICU setting, high pharmacokinetic variability, together with the variability of microbe susceptibility, led to poor predictability of PK/PD markers based on general population data [96].

Once we have a goal of therapy, the first step is to define the drug dose that has a high probability of delivering the desired target. The Monte Carlo simulation allows the calculation of the proportion of patients obtaining a specific degree of drug exposure. Afterward, the exposures are corrected for protein binding and the fraction of simulated

subjects who attained the pharmacodynamic target is calculated for each MIC in the distribution. Overall target attainment is then calculated by taking the product of the target attainment at a specific MIC and the fraction of organisms in the distribution at that MIC. All products are then summed, giving a weighted average target attainment rate that takes into account the variability in MICs as well as the variability in pharmacokinetic parameters across a specific population of patients. Finally, Bayesian estimation allows patient-specific estimation of drug exposure. This estimation process explicitly balances information about the specific patient (the drug concentrations obtained from that patient) with prior knowledge about how a specific patient population handles a particular drug. In this way, the best point estimates of the pharmacokinetic parameter values for each patient in the data set can be obtained, thus allowing calculation of the $C_{\max}/\text{MIC}$ ratio, AUC/MIC ratio or $T_{>\text{MIC}}$.

Several studies have confirmed that a Bayesian method may be helpful for individualizing dosing regimens of antimicrobials in the ICU setting [97,98]. Furthermore, since the physiology of ICU patients may change over a relatively short period, ongoing evaluation of sickness severity and therapeutic drug monitoring are strongly recommended to allow timely adjustment of antibacterial dosing. This should not only be achieved for antimicrobials that have plasma concentrations routinely monitored, but for all antimicrobials.

Every effort should be undertaken by clinicians, microbiologists and pharmacologists to improve the microbiological diagnosis and the PK/PD correlation. These efforts may result in a better clinical outcome and a reduction in antibiotic resistance levels and economic costs.

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[Figure legend]

Fig. 1. Mortality impact of inadequate antimicrobial therapy in bacteraemia. ^a Resistant Gram-negative microorganisms; ^b Community-acquired bacteraemia.

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