Critically Ill Patients Antimicrobial Dosing

In recent years, the knowledge of pharmacokinetics and pharmacodynamics, drug dosing, therapeutic drug monitoring, and antimicrobial resistance in the critically ill patients has greatly improved, fostering strategies to optimize therapeutic efficacy and to reduce toxicity and adverse events. Nonetheless, delivering adequate and appropriate antimicrobial therapy is still a challenge, since pathogen resistance continues to rise, and new therapeutic agents remain scarce.

1. Introduction

One of the recommendations from the Surviving Sepsis Campaign (SSC) is antibiotic therapy in the first hour [1]. This is a key element for successful sepsis management. However, for this to be effective, several decisions must be addressed simultaneously when prescribing antimicrobials (AM): (1) AM choices should be adequate, covering the most probable pathogens; (2) they should be administered in the appropriate dose, (3) by the correct route, and (4) using the correct mode of administration to achieve successful concentration at the infection site.

It is well known that inadequate empirical antibiotic therapy is associated with poor outcomes. However, there are scarce data concerning the impact of inadequate dosing on outcomes of critically ill patients [2][3]. Moreover, patients with sepsis and septic shock present an increased risk of underdosing, increased volume of distribution (Vd), increased clearance, risk of overdosing, and risk of renal and hepatic failure. In addition, we are facing infections frequently caused by pathogens with higher minimum inhibitory concentrations, consequently increasing the risk of inadequate dosing. In order to be effective, AM dosing should be optimized to quickly attain bactericidal concentrations at the infection site. To optimize the AM exposure of pathogens, it is also fundamental to consider drug penetration in different organs both in health and disease [4][5].

2. Pharmacokinetic and Pharmacodynamic Characteristics of Antimicrobials

The therapeutic window of a drug is defined according to previously studied dose–response relationships which will also determine the limits of safe concentration and dosage. The dose and duration of dosing intervals of AM are determined according to their pharmacokinetic/pharmacodynamic (PK/PD) properties [6]. However, in critical illness, multiple underlying derangements provoke pathophysiological alterations that change the PK/PD of drugs and therefore provoke dynamic changes in drug concentration.

Antimicrobials are classified according to their dose–response relationships into the following PK/PD groups: time-dependent, concentration-dependent, and concentration-dependent with time-dependence [6][7]. The effect of time-dependent AM, such as β-lactams, depends on the cumulative percentage of time over 24 h by which the free AM concentration exceeds the MIC (%fT > MIC). The killing rate does not improve if concentration greatly exceeds the MIC [8]. In concentration-dependent AM, such as aminoglycosides (AG), their effect depends on the peak concentration divided by the MIC (Peak/MIC). The higher the AM concentration, the greater the extent and rate of bactericidal activity [9]. Optimal Peak/MIC targets for AG will be further discussed in this review. The effect of concentration-dependent drugs with time-dependence, such as fluoroquinolones and glycopeptides, is determined by the AUC 0–24 h divided by the MIC, and specific targets, as will be further discussed, depend on the AM [6][9].

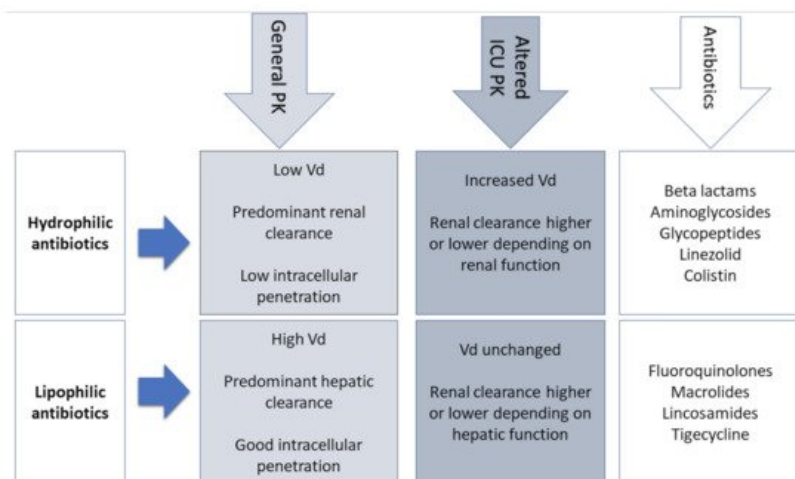The physicochemical properties of AM should also integrate the choice of appropriate dosing (**Figure 1**).

Figure 1. Physicochemical properties of antibiotics. Vd—Volume of distribution; PK—Pharmacokinetics.

In the ICU patient, traditional dosing strategies will most likely be insufficient to achieve the desired PK/PD targets of maximal AM activity. Therefore, an individualized approach considering specific MICs and regimens most likely to attain PK/PD goals can provide reasonable solutions.

3. PK Changes in Critically Ill Patients

Critically ill patients present important pathophysiological changes that significantly modify the PK of antimicrobials [10]. In septic shock, blood flow of gastrointestinal tract and subcutaneous tissue are severely reduced and shunted to vital organs such as the brain and heart, compromising reliable drug absorption with administration via these routes. As a result, intravenous administration of AM is always recommended in patients with sepsis and septic shock [1][10].

Patients with sepsis and septic shock present a significant fluid shift from the intravascular compartment to interstitial space due to endothelial damage and increased capillary leak. This leak results in severe hypotension requiring aggressive intravenous volume resuscitation that further increases the Vd, the eventual simultaneous prescription of vasopressors, and development of organ failures such as circulatory shock and renal failure (**Table 1**). For these reasons, hydrophilic AM (aminoglycosides, β-lactams, glycopeptides, and lipopeptides) with an extracellular distribution need a higher loading dose to achieve therapeutic concentrations [3][11]. On the other hand, the Vd of lipophilic antibiotics is not significantly influenced by these changes and does not require dose adjustments [12].

Table 1. Volume of distribution of ICU antibiotics.

Antibiotics that Stay in Extracellular Fluid (Vd < 0.3 L/kg)	Drugs that Distribute into Total Body Water (Vd 0.7–1 L/kg)	Drug with High Distribution to Tissues (Vd > 1 L/kg)
- Aminoglycosides		- Colistin
- Beta-lactams	- Clindamycin	- Fluoroquinolones
- Penicillins	- Linezolid	- Macrolides
- Cephalosporins	- Metronidazole	- Azithromycin
- Carbapenems	- Vancomycin	- Clarithromycin
- Daptomycin		- Tigecyline

Another important factor that can influence the Vd of AM is the modification in protein binding. Since albumin is the main plasma-binding protein for many AM (e.g., cefazolin, ceftriaxone, ertapenem, and daptomycin), its decreased concentration in septic patients has a direct impact on the PK of antibiotics [13]. With low plasma albumin, there is an increase of the unbound antibiotic, increasing its Vd and clearance, and leading to lower and probably suboptimal AM concentrations toward the end of dosing intervals. For these reasons, therapeutic drug monitoring (TDM) should include an adjustment for low albumin levels or a direct measurement of free drug levels [14].

4. Antibiotics in the ICU

4.1. B-Lactams

The β-lactams' broad spectrum of AM activity and low toxicity profiles unsurprisingly render them first-line options in serious infections, namely Gram-negative bacilli (GNB) infections, and the most commonly prescribed AM in critical care [15][16].

B-lactams are generally hydrophilic, with low Vd, moderate to low protein binding, and essentially renal excretion [17]. In vivo animal studies have clearly shown that β-lactams are characterized by a slow continuous kill, in other words, time-dependent bactericidal activity [18][19]. Consequently %fT > MIC is the optimal PK/PD parameter for β-lactams, with the recommended interval of 40–70% [17][20], varying according to the AM and underlying pathogens [21]. This time-dependent effect is independent of peak values and little post-antibiotic effect exists, except for carbapenems [22]. Since β-lactams have short or no post-antibiotic effect, when AM concentration falls below the MIC at the infection site, residual pathogens can rapidly regrow [23]. Furthermore, frequent Vd and Cl alterations accentuate the risk of suboptimal drug concentrations in the face of critical illness [17]. For example, with hypoalbuminemia, highly protein-bound β-lactams such as ceftriaxone, ertapenem, flucloxacillin, and oxacillin will present increased free fractions [24].

4.2. Aminoglycosides

Aminoglycosides are frequently prescribed as empirical therapy regimens in septic ICU patients, namely when suspicion of GNB infection prevails [25]. Furthermore, recent guidelines recommend combination therapy in septic shock [1]. The rationale for combination therapy originated from in vitro findings of synergistic bactericidal activity with certain combination therapies in the context of Pseudomonas aeruginosa and other GNB infections [26][27][28]. However, in a recent metanalysis comparing β-lactam monotherapy with β-lactam/aminoglycoside combination therapy, evidence regarding non-neutropenic septic patients does not show a mortality benefit with combination therapy [29].

Aminoglycosides are hydrophilic, with low Vd and drug clearance proportional to GFR [17]. Extended-interval dosing of a high, single dose is recommended in GNB infections.

4.3. Glycopeptides

Vancomycin

Most published data regarding vancomycin dosing and TDM are retrospective observational or PK/PD assessments, with few published RCT. Since the 2009 guidelines on the treatment of serious methicillin-resistant Staphylococcus aureus (MRSA) infections, new light has been shed regarding the efficacy and safety of previous recommendations [30]. Issues such as dosing strategies in obese patients, safety profiles in daily dosages exceeding 3 g, continuous infusion strategies, and renal failure are some examples where insufficient data precluded adequate coverage. Moreover, existing recommendations of exposure effectiveness are based mainly on studies of MRSA bacteriemia, with fewer studies of pneumonia and endocarditis. Nevertheless, much controversy around vancomycin dosing and TDM still exists [30].

Vancomycin is hydrophilic, has a low Vd, and elimination is mainly renal. Altered Vd and drug clearance, namely ARC, in the critically ill may lead to low drug exposure [17].

4.4. Colistin

Current guidelines for ventilator-associated pneumonia (VAP) recommend empirical combination therapy with colistin and another antipseudomonal AM in ICUs where carbapenem-resistant (CR) GNB are highly prevalent [31][32]. Recent meta-analyses evaluated the efficacy and safety of colistin for VAP caused by MDR GNB and found it to have similar efficacy and safety as seen with β-lactams. However, multiple limitations of the studies included call into question the strength of these findings [33][34][35].

4.5. Fluoroquinolones

The AM spectrum of fluoroquinolones includes GNB, Gram-positive, and with some, also anaerobic coverage, with popular use since the 1980s [36]. However, over the years, GNB resistance has drastically increased, with susceptibility rates less than 70% for agents such as Escherichia coli, Pseudomonas aeruginosa, and Proteus mirabilis [36][37]. Moreover, the frequent and inappropriate use of this class has been associated with Clostridium difficile infection outbreaks and the emergence of MRSA [38][39]. The issues related to fluoroquinolone resistance have led to their infrequent use as first-line AM in the ICU setting where GNB such as Pseudomonas aeruginosa, Acinetobacter baumannii,

and Stenotrophomonas maltophilia are often fluoroquinolone-resistant. However, when used in the ICU setting, fluoroquinolones should be administered at maximum doses (levofloxacin 750 mg every 24 h; ciprofloxacin 400 mg every 8 h) [36].

5. Strategies to Optimize Dosing

There is increasing evidence that front-line antibiotic inappropriateness is common and may have significant impact on the outcome of patients with severe infections and septic shock [16][22]. Large spectrum AM as well as combination therapy have both been proposed as strategies to enlarge antibacterial spectrum and improve patient outcomes [1]. However, appropriate spectrum of antibiotic therapy may be insufficient if adequate exposure is missed [3][40]. Early achievement of adequate antibiotic concentration is of paramount importance when treating patients with septic shock.

Promoting high peak concentration for concentration-dependent antibiotics (e.g., aminoglycosides), which is concentrating the daily dose on only one time-point, or, on the contrary, promoting long exposure time, for time-dependent antibiotics (e.g., penicillins), with prolonged or continuous infusions, was proposed to optimize therapeutic success [41]. However, these strategies may be flawed in the presence of PK changes: high concentration peaks may be toxic or, in contrast, inadequately low (especially in patients with a changing Vd), and the time between doses may not be enough to achieve adequate trough concentration. In addition, in the presence of altered clearance, the concentration of time-dependent antibiotics may always be under the adequate target or, alternately, it may accumulate and lead to toxic concentrations [3]. Conventional or nomogram-guided dosing may easily fail to achieve the intended target concentration. This has been demonstrated for vancomycin [42], aminoglycosides [43], daptomycin [44], linezolid [45], and also β-lactams [46][47]. Consequently, an interest in TDM has grown (**Table 2**).

Table 2. Pharmacokinetic and pharmacodynamic characteristics of common antibiotics in intensive care medicine [17].

Antimicrobial Class	Monitoring/ Sampling	PK/PD Target	Toxicity Threshold
Therapeutic Drug Monitoring Recommended			
Beta-lactams - Penicillins - Cephalosporins - Carbapenems	Cmin/One sample [1] Css (continuous infusion)/One sample [2]	100% fT> MIC Css > MIC 50–100% fT > MIC 45–100% fT > MIC 50–100% fT > MIC	Nephrotoxicity/Neurotoxicity Cmin > 361 mg/L (Piperacillin nephro-/neurotoxicity) Cmin > 20 mg/L (Cefepime neurotoxicity) Cmin > 44.5 mg/L (Meropenem nephro-/neurotoxicity)
Aminoglycosides - Gentamicin - Amikacin	AUC-based/Two samples [3] Cmax/MIC/One sample [4] Cmin/One sample [1]	AUC 80–120 mg h/L Cmax/MIC ≥ 8–10 Cmin <0.5 mg/L Cmin <2.5 mg/L	Nephrotoxicity/Ototoxicity Cmin> 1 mg/L Cmin> 5 mg/L
Glycopeptides - Vancomycin	AUC/MIC/Two samples [5] Cmin/One sample [1] Css/One sample [2]	AUC (0–24)/MIC ≥ 400 Cmin ≥ 15–20 mg/L [6] Css 20–25 mg/L	Nephrotoxicity Cmin > 20 mg/L
Therapeutic Drug Monitoring Neither Recommended nor Discouraged			
Colistin	Cmin/One sample [1] AUC (0–24)/MIC	Cmin 2 mg/L Not defined	Nephrotoxicity Cmin > 2.4 mg/L
Fluoroquinolones	AUC/MIC/Two samples [7] Cmax/MIC/One sample [4]	fAUC0–24/MIC ≥ 80 Cmax/MIC ≥ 8–12	Not defined

[1] 30 min or just before next dosing. [2] One sample at any time point during the infusion. [3] One 30 min after the end of infusion and another 6–22 h after infusion. [4] 30 min after the end of infusion. [5] 1 h after the end of infusion and another within 1–2 h of the next infusion. [6] For severe infections. [7] 2 h after dosing and the other 6 h after dosing; Cmin trough drug concentration; MIC minimum inhibitory concentration; fT > MIC percentage of time over 24 h that the free antimicrobial concentration exceeds the MIC; Css average steady-state drug concentration; AUC area under the

concentration–time curve; Cmax/MIC ratio of maximum drug concentration to minimum inhibitory concentration; AUC/MIC ratio of the area under the concentration–time curve during a 24 h period to minimum inhibitory concentration.

The potential benefits of TDM are mainly related to the existence of a recognized relationship between serum drug concentration and the intended effect. The same is especially relevant when there is a narrow therapeutic index. Moreover, clinical benefits also rely on the existence of a standardized, easily operated, and unexpensive method to reliably measure drug concentrations, with a high intra and intercenter reproducibility, a short turnaround time (allowing real-time dosing adjustment), and a simplified sampling strategy that facilitates dose adjustment.

Recently published papers strongly advocate using TDM to optimize dosing of AM not only for AG and vancomycin but also for β-lactams, daptomycin, and teicoplanin (along with antifungals and antivirals) [17]. The rapid increase in bacteria resistance to available antibiotics, as well as emerging PK data unveiling that commonly used antibiotic doses may easily lead to low antibiotic concentrations [22][48] as well as the existence of a PK intra-patient variability throughout treatment course [2][49][50], suggest that benefits may extend to these AM.

In clinical practice, the major benefit of rapid antibiotic bacteria killing seems to be mostly concentrated in the first days of therapy. Using timely administered high antibiotic doses after sepsis diagnosis seems to be of utmost importance. Consequently, avoiding antibiotic delay [51][52], using PK and PD principles to guide antibiotic dosing, such as achieving a high peak of concentration-dependent antibiotics and using extended infusions of time-dependent antibiotics [53] during the first 48 h of therapy, is probably safe and may improve clinical outcomes. After achieving adequate sepsis control, when the patient is improving and the bacteria inoculum is reduced, the prevention of overexposure and potential toxicity [54][55] should also become a priority.

6. Other Approaches to Optimize Dosing–Nebulization

The increased prevalence of VAP caused by MDR pathogens, the poor lung penetration of commonly prescribed AM, and the absence of new AM in the pipeline led clinicians to search for alternative approaches to optimize drug dosing in the lung, of which the use of inhaled antibiotics is the most used and studied approach [5][56][57][58].

Nebulized antibiotics have been used with two aims: as an alternative to IV antibiotics and as an adjunctive therapy in addition to IV. The main aim of this strategy is to achieve good antibiotic concentrations at the lung parenchyma, minimizing systemic effects: namely toxicity, antibiotic pressure, and the rate of emergence of MDR pathogens [59]. The use of nebulized antibiotics as an isolated therapy in pneumonia (as an alternative to the IV route) cannot be recommended, since there are no data to support this strategy. Moreover, 10–20% of VAP present secondary bacteremia that would not be adequately treated with this approach [31].

There are also some potential benefits from this approach, namely the decrease in the emergence of MDR pathogens. Since the epithelial lining fluid concentrations attained with nebulization are frequently well above MIC, such high levels in the lung might contribute to decreasing the risk of emergence of drug resistance [60]. Although controversial, this has been suggested in two studies in patients with ventilator-associated tracheobronchitis [59][61] but without robust data from the recent RCTs.

7. Impact of Dosing Strategies on Outcomes

Bacteria killing by antibiotics is closely linked to exposure. According to the PK/PD relationship, antibiotics' killing is mostly related to the time above bacteria MIC (T > MIC) or peak concentration/bacteria MIC (Peak/MIC) (**Figure 2**). In a series of landmark studies, ideal exposure was calculated as T > MIC of roughly 40–60% (for β-lactams), ratio of AUC/MIC of 30–40 (Gram positive) or 120 (GNB) for fluroquinolones, and Peak/MIC 8–10 for aminoglycosides [9][21][62]. However, the majority of these studies rely mostly on retrospective data, and in vivo evidence is still poor and sometimes conflicting, especially when referring to β-lactams [63][64].
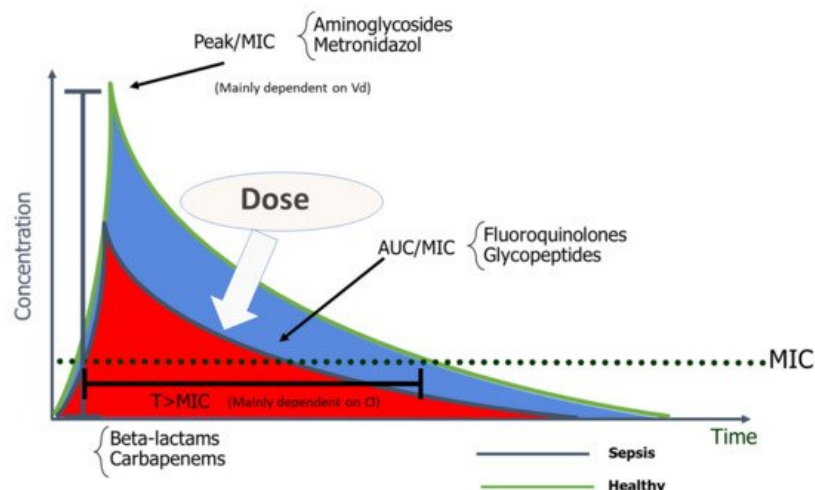
Figure 2. Pharmacokinetics and pharmacodynamics: After an antibiotic infusion, a ratio between the peak concentration and the minimal inhibitory concentration, the area under the concentration–time curve and the minimal inhibitory concentration, and the time the antibiotic concentration is above the minimal inhibitory concentration can be defined. These three parameters all decreased in septic patients, with an increased volume of distribution and clearance. The only secure way to achieve effective antibiotic concentration is to adjust the dose. MIC—minimal inhibitory concentration; T > MIC—time that the antibiotic concentration is above the minimal inhibitory concentration; Vd—Vole of distribution; Cl—Clearance.

It should also be noted that in clinical practice, patients with renal failure, a well-known risk factor for worse outcome and mortality, often easily achieve higher and prolonged antibiotic exposure [65][66][67]. Consequently, there may be a significant interaction between this high antibiotic exposure and the high-risk clinical status, which may limit the evaluation of the potential benefit of adequate antibiotic exposure. Moreover, bacteria killing is a biologic (and not mechanical) process and significant inter-patient and intra-patient in vivo variability may be noted [68][69].

Optimization of dosing strategies for each particular antibiotic in any single patient may help to improve clinical and microbiological outcome. Increasing the time of exposure of β-lactams as well as achieving high exposures of fluoroquinolones and peak concentrations of AG are associated with optimal bacterial killing in vitro [23][21].

In critically ill patients, higher targets have been proposed, especially for β-lactams, including a time of 100% over a concentration as high as 4*MIC [70][67].

The limited available data concerning the relationship between PK/PD targets and outcomes should not be viewed as proof of lack of benefit. Absence of evidence of benefit does not equal evidence of absence of benefit. While the attainment of any antibiotic concentration target does not guarantee per se efficacy or an improved outcome for any single patient, using individually guided dosing optimizes the probability of achieving a numerically higher favorable response in a whole population [68]. Variability in targets (such as the organism's MIC) can be considered in models with subsequent adaptation as new information arrives. That is, complexity alone should not relegate the decision-making process to clinician guessing. The exposure–response relationship is necessarily complex, and it is modified by patient, bacteria, and the focus of infection-specific factors. Information regarding precision dosing should inform clinical decision making rather than protocolize it in an absolute mode [68].

8. Future Directions and Conclusions

Several factors contribute to the success of infection management in critically ill patients. In addition to the adequacy of empiric AM therapy, optimizing dosing is also crucial, namely the prescribed dose, the route, and the mode of administration. This is particularly challenging in critically ill patients due to PK changes related to the unpredictable Vd as well as degree of organ failure, both renal and liver, but also ARC. As a result, to attain target concentrations, the current recommendations point to higher doses of AM in the first days with TDM whenever possible.

Future research should address some unmet needs, namely TDM of different AM, as well as defining target concentrations, assessing the correlation between serum and tissue concentrations of AM, optimizing AM dosing during the course of the infection and according to disease severity, among others, that could improve several clinical outcomes in an era of increasing MDR pathogens.

Meanwhile, we must use the available tools to optimize individual AM dosing to maximize the exposure and effectiveness of these drugs in critically ill patients.

References

1. Rhodes, A.; Evans, L.E.; Alhazzani, W.; Levy, M.M.; Antonelli, M.; Ferrer, R.; Kumar, A.; Sevransky, J.E.; Sprung, C.L.; Nunnally, M.E.; et al. Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016. Intensive Care Med. 2017, 43, 304–377.

2. Goncalves-Pereira, J.; Paiva, J.A. Dose modulation: A new concept of antibiotic therapy in the critically ill patient? J. Crit. Care 2013, 28, 341–346.

3. Roberts, J.A.; Abdul-Aziz, M.H.; Lipman, J.; Mouton, J.W.; Vinks, A.A.; Felton, T.W.; Hope, W.W.; Farkas, A.; Neely, M.N.; Schentag, J.J.; et al. Individualised antibiotic dosing for patients who are critically ill: Challenges and potential solutions. Lancet Infect. Dis. 2014, 14, 498–509.

4. Ulldemolins, M.; Roberts, J.A.; Lipman, J.; Rello, J. Antibiotic dosing in multiple organ dysfunction syndrome. Chest 2011, 139, 1210–1220.

5. Jamal, W.; Al Roomi, E.; AbdulAziz, L.R.; Rotimi, V.O. Evaluation of Curetis Unyvero, a multiplex PCR-based testing system, for rapid detection of bacteria and antibiotic resistance and impact of the assay on management of severe nosocomial pneumonia. J. Clin. Microbiol. 2014, 52, 2487–2492.

6. Blot, S.I.; Pea, F.; Lipman, J. The effect of pathophysiology on pharmacokinetics in the critically ill patient--concepts appraised by the example of antimicrobial agents. Adv. Drug Deliv. Rev. 2014, 77, 3–11.

7. Roberts, J.A.; Lipman, J. Pharmacokinetic issues for antibiotics in the critically ill patient. Crit. Care Med. 2009, 37, 840–851.

8. Mouton, J.W.; Punt, N.; Vinks, A.A. Concentration-effect relationship of ceftazidime explains why the time above the MIC is 40 percent for a static effect in vivo. Antimicrob. Agents Chemother. 2007, 51, 3449–3451.

9. Craig, W.A. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. Clin. Infect. Dis. 1998, 26, 1–10.

10. Smith, B.S.; Yogaratnam, D.; Levasseur-Franklin, K.E.; Forni, A.; Fong, J. Introduction to drug pharmacokinetics in the critically ill patient. Chest 2012, 141, 1327–1336.

11. Varghese, J.M.; Roberts, J.A.; Lipman, J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. Crit. Care Clin. 2011, 27, 19–34.

12. Gous, A.; Lipman, J.; Scribante, J.; Tshukutsoane, S.; Hon, H.; Pinder, M.; Mathivha, R.; Verhoef, L.; Stass, H. Fluid shifts have no influence on ciprofloxacin pharmacokinetics in intensive care patients with intra-abdominal sepsis. Int. J. Antimicrob. Agents 2005, 26, 50–55.

13. Ulldemolins, M.; Roberts, J.A.; Rello, J.; Paterson, D.L.; Lipman, J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin. Pharmacokinet. 2011, 50, 99–110.

14. SAFE Study Investigators; Finfer, S.; Bellomo, R.; McEvoy, S.; Lo, S.K.; Myburgh, J.; Neal, B.; Norton, R. Effect of baseline serum albumin concentration on outcome of resuscitation with albumin or saline in patients in intensive care units: Analysis of data from the saline versus albumin fluid evaluation (SAFE) study. BMJ 2006, 333, 1044.

15. Williams, P.; Cotta, M.O.; Roberts, J.A. Pharmacokinetics/Pharmacodynamics of beta-Lactams and Therapeutic Drug Monitoring: From Theory to Practical Issues in the Intensive Care Unit. Semin Respir Crit. Care Med. 2019, 40, 476–487.

16. Goncalves-Pereira, J.; Povoa, P. Antibiotics in critically ill patients: A systematic review of the pharmacokinetics of beta-lactams. Crit. Care 2011, 15, R206.

17. Abdul-Aziz, M.H.; Alffenaar, J.C.; Bassetti, M.; Bracht, H.; Dimopoulos, G.; Marriott, D.; Neely, M.N.; Paiva, J.A.; Pea, F.; Sjovall, F.; et al. Antimicrobial therapeutic drug monitoring in critically ill adult patients: A Position Paper. Intensive Care Med. 2020, 46, 1127–1153.

18. Andes, D.; Craig, W.A. In vivo activities of amoxicillin and amoxicillin-clavulanate against Streptococcus pneumoniae: Application to breakpoint determinations. Antimicrob. Agents Chemother. 1998, 42, 2375–2379.

19. Mouton, J.W.; Punt, N. Use of the t > MIC to choose between different dosing regimens of beta-lactam antibiotics. J. Antimicrob. Chemother. 2001, 47, 500–501.

20. Craig, W.A. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. Infect. Dis. Clin. N. Am. 2003, 17, 479–501.

21. Drusano, G.L. Antimicrobial pharmacodynamics: Critical interactions of 'bug and drug'. Nat. Rev. Microbiol. 2004, 2, 289–300.

22. Taccone, F.S.; Laterre, P.F.; Dugernier, T.; Spapen, H.; Delattre, I.; Wittebole, X.; De Backer, D.; Layeux, B.; Wallemacq, P.; Vincent, J.L.; et al. Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. Crit. Care 2010, 14, R126.

23. Pea, F.; Viale, P.; Furlanut, M. Antimicrobial therapy in critically ill patients: A review of pathophysiological conditions responsible for altered disposition and pharmacokinetic variability. Clin. Pharmacokinet. 2005, 44, 1009–1034.

24. Roberts, J.A.; Pea, F.; Lipman, J. The clinical relevance of plasma protein binding changes. Clin. Pharmacokinet. 2013, 52, 1–8.

25. Roger, C.; Louart, B.; Elotmani, L.; Barton, G.; Escobar, L.; Koulenti, D.; Lipman, J.; Leone, M.; Muller, L.; Boutin, C.; et al. An international survey on aminoglycoside practices in critically ill patients: The AMINO III study. Ann. Intensive Care 2021, 11, 49.

26. Giamarelloum, H. Aminoglycosides plus beta-lactams against gram-negative organisms. Evaluation of in vitro synergy and chemical interactions. Am. J. Med. 1986, 80, 126–137.

27. Giamarellou, H.; Zissis, N.P.; Tagari, G.; Bouzos, J. In vitro synergistic activities of aminoglycosides and new beta-lactams against multiresistant Pseudomonas aeruginosa. Antimicrob. Agents Chemother. 1984, 25, 534–536.

28. Klastersky, J.; Meunier-Carpentier, F.; Prevost, J.M.; Staquet, M. Synergism between amikacin and cefazolin against Klebsiella: In vitro studies and effect on the bactericidal activity of serum. J. Infect. Dis. 1976, 134, 271–276.

29. Paul, M.; Lador, A.; Grozinsky-Glasberg, S.; Leibovici, L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. Cochrane Database Syst. Rev. 2014.

30. Rybak, M.J.; Le, J.; Lodise, T.P.; Levine, D.P.; Bradley, J.S.; Liu, C.; Mueller, B.A.; Pai, M.P.; Wong-Beringer, A.; Rotschafer, J.C.; et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am. J. Health Syst. Pharm. 2020, 77, 835–864.

31. Kalil, A.C.; Metersky, M.L.; Klompas, M.; Muscedere, J.; Sweeney, D.A.; Palmer, L.B.; Napolitano, L.M.; O'Grady, N.P.; Bartlett, J.G.; Carratala, J.; et al. Management of Adults with Hospital-acquired and Ventilator-associated Pneumonia: 2016 Clinical Practice Guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin. Infect. Dis. 2016, 63, e61–e111.

32. Torres, A.; Niederman, M.S.; Chastre, J.; Ewig, S.; Fernandez-Vandellos, P.; Hanberger, H.; Kollef, M.; Li Bassi, G.; Luna, C.M.; Martin-Loeches, I.; et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia: Guidelines for the management of hospital-acquired pneumonia (HAP)/ventilator-associated pneumonia (VAP) of the European Respiratory Society (ERS), European Society of Intensive Care Medicine (ESICM), European Society of Clinical Microbiology and Infectious Diseases (ESCMID) and Asociacion Latinoamericana del Torax (ALAT). Eur. Respir. J. 2017.

33. Gu, W.J.; Wang, F.; Tang, L.; Bakker, J.; Liu, J.C. Colistin for the treatment of ventilator-associated pneumonia caused by multidrug-resistant Gram-negative bacteria: A systematic review and meta-analysis. Int. J. Antimicrob. Agents 2014, 44, 477–485.

34. Tulli, G.; Messori, A.; Trippoli, S.; Marinai, C. Non-inferiority of colistin compared with standard care for the treatment of ventilator-associated pneumonia. Int. J. Antimicrob. Agents 2017, 49, 638–641.

35. Florescu, D.F.; Qiu, F.; McCartan, M.A.; Mindru, C.; Fey, P.D.; Kalil, A.C. What is the efficacy and safety of colistin for the treatment of ventilator-associated pneumonia? A systematic review and meta-regression. Clin. Infect. Dis. 2012, 54, 670–680.

36. Rotschafer, J.C.; Ullman, M.A.; Sullivan, C.J. Optimal use of fluoroquinolones in the intensive care unit setting. Crit. Care Clin. 2011, 27, 95–106.

37. Mihu, C.N.; Rhomberg, P.R.; Jones, R.N.; Coyle, E.; Prince, R.A.; Rolston, K.V. Escherichia coli resistance to quinolones at a comprehensive cancer center. Diagn. Microbiol. Infect. Dis. 2010, 67, 266–269.

38. Graffunder, E.M.; Venezia, R.A. Risk factors associated with nosocomial methicillin-resistant Staphylococcus aureus (MRSA) infection including previous use of antimicrobials. J. Antimicrob. Chemother. 2002, 49, 999–1005.

39. Pepin, J.; Saheb, N.; Coulombe, M.A.; Alary, M.E.; Corriveau, M.P.; Authier, S.; Leblanc, M.; Rivard, G.; Bettez, M.; Primeau, V.; et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhe

a: A cohort study during an epidemic in Quebec. Clin. Infect. Dis. 2005, 41, 1254–1260.

40. Kollef, M.H. Antibiotics for the critically ill: More than just selecting appropriate initial therapy. Crit. Care 2013, 17, 146.

41. Udy, A.A.; Roberts, J.A.; Lipman, J. Clinical implications of antibiotic pharmacokinetic principles in the critically ill. Intensive Care Med. 2013, 39, 2070–2082.

42. Pea, F.; Bertolissi, M.; Di Silvestre, A.; Poz, D.; Giordano, F.; Furlanut, M. TDM coupled with Bayesian forecasting should be considered an invaluable tool for optimizing vancomycin daily exposure in unstable critically ill patients. Int. J. Antimicrob. Agents 2002, 20, 326–332.

43. Goncalves-Pereira, J.; Martins, A.; Povoa, P. Pharmacokinetics of gentamicin in critically ill patients: Pilot study evaluating the first dose. Clin. Infect. Dis. 2010, 16, 1258–1263.

44. Galar, A.; Munoz, P.; Valerio, M.; Cercenado, E.; Garcia-Gonzalez, X.; Burillo, A.; Sanchez-Somolinos, M.; Juarez, M.; Verde, E.; Bouza, E. Current use of daptomycin and systematic therapeutic drug monitoring: Clinical experience in a tertiary care institution. Int. J. Antimicrob. Agents 2019, 53, 40–48.

45. Galar, A.; Valerio, M.; Munoz, P.; Alcala, L.; Garcia-Gonzalez, X.; Burillo, A.; Sanjurjo, M.; Grau, S.; Bouza, E. Systematic Therapeutic Drug Monitoring for Linezolid: Variability and Clinical Impact. Antimicrob. Agents Chemother. 2017, 61.

46. Wong, G.; Sime, F.B.; Lipman, J.; Roberts, J.A. How do we use therapeutic drug monitoring to improve outcomes from severe infections in critically ill patients? BMC Infect Dis 2014, 14, 288.

47. Dhaese, S.A.M.; Thooft, A.D.J.; Farkas, A.; Lipman, J.; Verstraete, A.G.; Stove, V.; Roberts, J.A.; De Waele, J.J. Early target attainment of continuous infusion piperacillin/tazobactam and meropenem in critically ill patients: A prospective observational study. J. Crit. Care 2019, 52, 75–79.

48. Lipman, J.; Wallis, S.C.; Boots, R.J. Cefepime versus cefpirome: The importance of creatinine clearance. Anesth. Analg. 2003, 97, 1149–1154.

49. Goncalves-Pereira, J.; Silva, N.E.; Mateus, A.; Pinho, C.; Povoa, P. Assessment of pharmacokinetic changes of meropenem during therapy in septic critically ill patients. BMC Pharmacol. Toxicol. 2014, 15, 21.

50. De Waele, J.J.; Carrette, S.; Carlier, M.; Stove, V.; Boelens, J.; Claeys, G.; Leroux-Roels, I.; Hoste, E.; Depuydt, P.; De cruyenaere, J.; et al. Therapeutic drug monitoring-based dose optimisation of piperacillin and meropenem: A randomised controlled trial. Intensive Care Med. 2014, 40, 380–387.

51. Kumar, A.; Roberts, D.; Wood, K.E.; Light, B.; Parrillo, J.E.; Sharma, S.; Suppes, R.; Feinstein, D.; Zanotti, S.; Taiberg, L.; et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. Crit. Care Med. 2006, 34, 1589–1596.

52. Leisman, D.; Huang, V.; Zhou, Q.; Gribben, J.; Bianculli, A.; Bernshteyn, M.; Ward, M.F.; Schneider, S.M. Delayed Second Dose Antibiotics for Patients Admitted from the Emergency Department with Sepsis: Prevalence, Risk Factors, and Outcomes. Crit. Care Med. 2017, 45, 956–965.

53. Lipman, J.; Roberts, J. Does Appropriate Antibiotic Therapy Mean Only Adequate Spectrum and Timing? Crit. Care Med. 2015, 43, 1773–1774.

54. Arulkumaran, N.; Routledge, M.; Schlebusch, S.; Lipman, J.; Conway Morris, A. Antimicrobial-associated harm in critical care: A narrative review. Intensive Care Med. 2020, 46, 225–235.

55. Beumier, M.; Casu, G.S.; Hites, M.; Wolff, F.; Cotton, F.; Vincent, J.L.; Jacobs, F.; Taccone, F.S. Elevated beta-lactam concentrations associated with neurological deterioration in ICU septic patients. Minerva Anestesiol. 2015, 81, 497–506.

56. Drusano, G.L. What are the properties that make an antibiotic acceptable for therapy of community-acquired pneumonia? J. Antimicrob. Chemother. 2011, 66 (Suppl. S3), iii61–iii67.

57. Sweeney, D.A.; Kalil, A.C. Why don't we have more inhaled antibiotics to treat ventilator-associated pneumonia? Clin. Microbiol. Infect. 2019, 25, 1195–1199.

58. Sweeney, D.A.; Kalil, A.C. The last breath for inhaled antibiotics and VAP? Not so fast. Lancet Infect. Dis. 2020, 20, 265–266.

59. Palmer, L.B.; Smaldone, G.C. Reduction of bacterial resistance with inhaled antibiotics in the intensive care unit. Am. J. Respir. Crit. Care Med. 2014, 189, 1225–1233.

60. Schreiber, M.P.; Shorr, A.F. Inhaled antibiotics for the treatment of pneumonia. Curr. Opin. Pulm. Med. 2019, 25, 289–293.

61. Palmer, L.B.; Smaldone, G.C.; Chen, J.J.; Baram, D.; Duan, T.; Monteforte, M.; Varela, M.; Tempone, A.K.; O'Riordan, T.; Daroowalla, F.; et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. Crit. Care Med. 2008, 36, 2008–2013.

62. Ambrose, P.G.; Bhavnani, S.M.; Rubino, C.M.; Louie, A.; Gumbo, T.; Forrest, A.; Drusano, G.L. Pharmacokinetics-pharmacodynamics of antimicrobial therapy: It's not just for mice anymore. Clin. Infect. Dis. 2007, 44, 79–86.

63. Roberts, J.A. Using PK/PD to optimize antibiotic dosing for critically ill patients. Curr. Pharm Biotechnol. 2011, 12, 2070–2079.

64. Roberts, J.A.; Roberts, M.S.; Semark, A.; Udy, A.A.; Kirkpatrick, C.M.; Paterson, D.L.; Roberts, M.J.; Kruger, P.; Lipman, J. Antibiotic dosing in the 'at risk' critically ill patient: Linking pathophysiology with pharmacokinetics/pharmacodynamics in sepsis and trauma patients. BMC Anesthesiol. 2011, 11, 3.

65. Richter, D.C.; Frey, O.; Rohr, A.; Roberts, J.A.; Koberer, A.; Fuchs, T.; Papadimas, N.; Heinzel-Gutenbrunner, M.; Brenner, T.; Lichtenstern, C.; et al. Therapeutic drug monitoring-guided continuous infusion of piperacillin/tazobactam significantly improves pharmacokinetic target attainment in critically ill patients: A retrospective analysis of four years of clinical experience. Infection 2019, 47, 1001–1011.

66. Shekar, K.; Fraser, J.F.; Smith, M.T.; Roberts, J.A. Pharmacokinetic changes in patients receiving extracorporeal membrane oxygenation. J. Crit. Care 2012, 27, 741.

67. Abdulla, A.; Dijkstra, A.; Hunfeld, N.G.M.; Endeman, H.; Bahmany, S.; Ewoldt, T.M.J.; Muller, A.E.; van Gelder, T.; Gommers, D.; Koch, B.C.P. Failure of target attainment of beta-lactam antibiotics in critically ill patients and associated risk factors: A two-center prospective study (EXPAT). Crit. Care 2020, 24, 558.

68. Scheetz, M.H.; Lodise, T.P.; Downes, K.J.; Drusano, G.; Neely, M. The case for precision dosing: Medical conservatism does not justify inaction. J. Antimicrob. Chemother. 2021.

69. Carlier, M.; Carrette, S.; Stove, V.; Verstraete, A.G.; De Waele, J.J. Does consistent piperacillin dosing result in consistent therapeutic concentrations in critically ill patients? A longitudinal study over an entire antibiotic course. Int. J. Antimicrob. Agents 2014, 43, 470–473.

70. McKinnon, P.S.; Paladino, J.A.; Schentag, J.J. Evaluation of area under the inhibitory curve (AUIC) and time above the minimum inhibitory concentration (T>MIC) as predictors of outcome for cefepime and ceftazidime in serious bacterial infections. Int. J. Antimicrob. Agents 2008, 31, 345–351.