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The effect of pathophysiology on pharmacokinetics in the critically ill patient — Concepts appraised by the example of antimicrobial agents ☆

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ABSTRACT

Critically ill patients are at high risk for development of life-threatening infection leading to sepsis and multiple organ failure. Adequate antimicrobial therapy is pivotal for optimizing the chances of survival. However, efficient dosing is problematic because pathophysiological changes associated with critical illness impact on pharmacokinetics of mainly hydrophilic antimicrobials. Concentrations of hydrophilic antimicrobials may be increased because of decreased renal clearance due to acute kidney injury. Alternatively, antimicrobial concentrations may be decreased because of increased volume of distribution and augmented renal clearance provoked by systemic inflammatory response syndrome, capillary leak, decreased protein binding and administration of intravenous fluids and inotropes. Often multiple conditions that may influence pharmacokinetics are present at the same time thereby excessively complicating the prediction of adequate concentrations. In general, conditions leading to underdosing are predominant. Yet, since prediction of serum concentrations remains difficult, therapeutic drug monitoring for individual fine-tuning of antimicrobial therapy seems the way forward.

Contents

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1. Introduction

Dose–response relationships are indispensible to determine the therapeutic window of a drug and to define safe and deleterious concentrations and dosages. In general, these studies are conducted in healthy volunteers after which dosing is fine-tuned in mild-to-moderately ill patients. Results from these trials are frequently extrapolated for the use in critically ill patients. Such extrapolations presume comparable drug pharmacokinetics (PK) and pharmacodynamics (PD) in critically ill patients compared to patients with rather mild illness. Yet, critically ill patients may demonstrate multiple organ derangements inciting pathophysiological changes that can affect PK/PD properties of drugs. These changes can occur within an individual patient and may deviate according to the varying stages of illness. As such dosages being adequate at a given day may become inadequate some days later because of alterations in disease severity. In addition, critically ill patients usually receive a wide range of drugs thereby adding to the possibility of drug–drug interactions. Commonly prescribed drugs in intensive care units (ICUs) include sedatives and analgesics, anticoagulants, immunosuppressive and anticonvulsive agents, drugs with cardiovascular activity, and antimicrobials.

Basically the general principles of PK include absorption, distribution, metabolism, and elimination. Critical illness affects all of these processes thereby significantly influencing the PK of drugs [1]. Absorption refers to the process by which a drug leaves the site of administration (either by the enteral route, inhalation, topical, subcutaneously, intramuscular, or rectal) and concentrates in the circulation thereby representing the bioavailability. The amount of drug absorbed depends on drug characteristics (physicochemical properties, particle size, solubility, etc.) and properties of the organ/tissue of drug administration. For example, regarding enterally administered drugs, shock will reduce regional blood flow and motility, resulting in delayed gastric emptying and diminished absorption [2]. The use of vasopressors to restore arterial blood pressure will not per se normalize regional perfusion as these drugs have differing effects on organ vascular beds and notably on splanchnic blood flow. Alternatively, during shock or use of vasopressors skin perfusion will be reduced thereby decreasing absorption of subcutaneously administered drugs. Because of the issues of absorption intravenous drug administration is usually recommended during critical illness [3].

Volume of distribution (Vd) describes the relationship between dose and the resulting serum concentration. Critical illness and a plethora of associated interventions affect the distribution of drugs. Sepsis, shock, burn injury, pancreatitis, and alterations in plasma protein binding are just a few examples of disease entities influencing Vd. Alternatively fluid resuscitation, as frequently necessary in critically ill patients will also lead to increased Vd.

Drug metabolism occurs predominantly in the liver. The ability of the liver to clear drugs is proportionate to blood flow and/or the hepatic extraction ratio of the drug, mainly driven by the cytochrome P450 enzyme system [1]. Critical illness affects metabolic activity by alterations in plasma protein concentration, hepatic enzymatic activity and blood flow [4,5]. Additionally, many drugs used in critically ill patients may either induce or inhibit the activity of the various isoenzymes included in the cytochrome P450 complex.

Finally the elimination process can be disturbed during critical illness as renal clearance can be either enhanced or impaired. Augmented renal clearance can be driven by sepsis, burn injury, or use of inotropic agents [6]. On the other hand, acute kidney injury may complicate the ICU course [7,8]. Acute kidney injury may represent partial or complete loss of renal function. In the latter case renal replacement therapy will be necessary.

In the rest of this article we particularly focus on alterations in PK of antimicrobials in critically ill patients. In this regard antimicrobials are of extreme interest because (i) their PK is particularly vulnerable for the pathophysiological alteration during critical illness, (ii) dosing is not titrated to an immediately observed effect, and finally (iii) underdosing is associated with insufficient bacterial eradication and as such with bad outcome, while overdosing may provoke additional organ failure in a patient population already at increased risk for organ derangements. As such, the objective of this review is to summarize pathophysiological changes that may take place during critical illness, and their effect on pharmacokinetics of antimicrobials.

2. Infection and sepsis in the critically ill

Critically ill patients are at an increased risk for severe infection because of the extensive use of invasive devices for diagnoses and therapy, and because of their weakened physical condition [9]. Large point-prevalence studies indicated that 40% to 50% of critically patients experience infection during their intensive care unit (ICU) course [10,11].

Serious infections, such as bacteremia or pneumonia, incite a systemic inflammatory response syndrome (SIRS) indicating that the infectious process goes beyond local inflammation and affects the total organism. SIRS is part of the innate immune response and is, as per definition, characterized by the presence of at least two of the following conditions: fever or hypothermia, leukocytosis or leukopenia, tachycardia, tachypnoea, and hypotension [12]. Infections provoking SIRS produce the syndrome called sepsis. According to the level of severity a categorization is made between sepsis, severe sepsis and septic shock. Severe sepsis is associated with organ failure, while septic shock is accompanied by hypotension refractory to adequate fluid administration and necessitating vasopressor support.

The mortality rate associated with sepsis is approximately 20% to 30%, while mortality in patients with severe sepsis is about 30% to 50% [13,14]. An important proportion of this mortality rate is due to overall severity of acute illness and underlying disease [15,16]. The broad window of mortality can be explained by differences in source of infection [11], patients' age and underlying pathology (e.g. neutropenic patients) [17,18], microbial etiology and antimicrobial susceptibility patterns [19,20], associated organ failures [14,21], and adequacy of antimicrobial therapy. Prompt initiation of antimicrobial therapy limits the attributable mortality [22], but nevertheless outcomes often remain unacceptably grim and it has been hypothesized that the optimization of drug exposure might be the way forward in critically ill patients [23–25].

3. Defining adequate antimicrobial therapy

For antimicrobial therapy to be adequate, three requirements need to be fulfilled. First, the antimicrobial agent(s) should be initiated as soon as possible after the onset of sepsis [26,27]. In general this is before the causative pathogen is known. Second, as therapy is to be initiated empirically, the antimicrobial spectrum of the agent should be broad enough to cover the potential causative microorganisms [28,29]. Finally, appropriate antimicrobial dosing is required to maximize microbial killing, minimize the development of multidrug antimicrobial resistance, and avoid concentration-related adverse drug reactions [30–32].

While in the 1990s and the early 2000s there was a clear emphasis in the literature on the importance of empirically selecting the appropriate antimicrobial agent; in the recent years more attention has been given to the issue of adequate dosing. In mild-to-moderately ill patients target antimicrobial concentrations are achieved with standard dosages, as pharmacokinetics are relatively stable and foreseeable. As already mentioned however, in critically ill patients, PK is prone to a variety of pathophysiological alterations, thereby complicating optimal dosing.

4. Physicochemical properties of antimicrobial agents

The choice of appropriate antimicrobial dosing in critically ill patients is greatly affected by the intrinsic physicochemical properties of the drugs [33]. As a general rule, clinicians must be aware of the fact

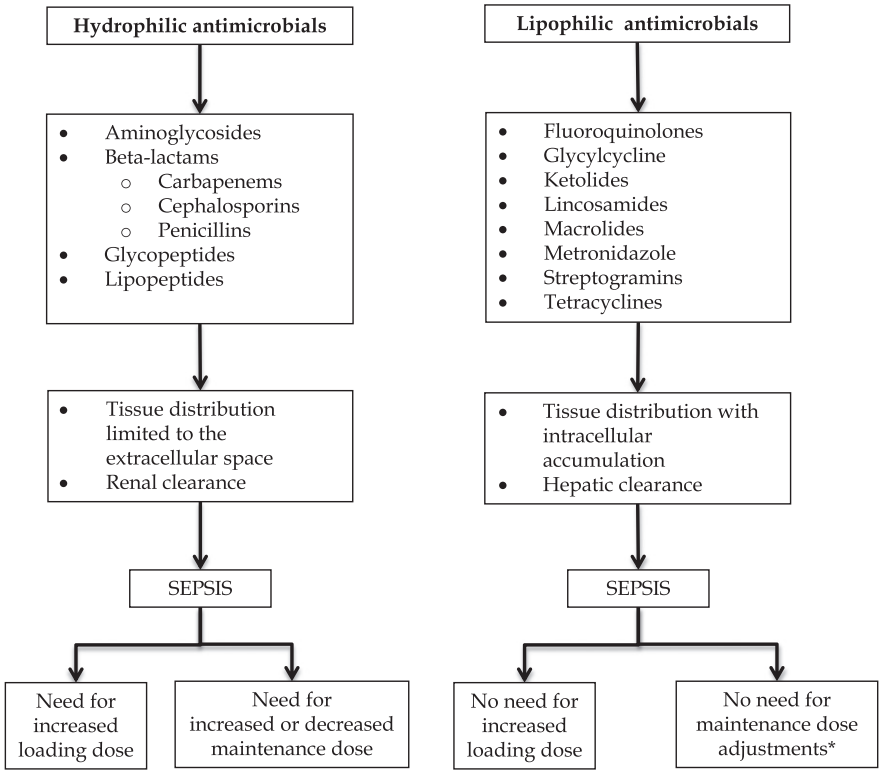


Fig. 1. Physicochemical properties of antimicrobials and dosage requirements in the presence of severe sepsis. *Need for dose reductions only indicated in case of severe hepatic failure.

that it's especially the PK of hydrophilic antimicrobials (Fig. 1) that may be affected by the presence of sepsis. This is in relation with the limited tissue distribution of these agents which is normally restricted to the extracellular space, so that significant antibiotic dilution might occur whenever intravascular fluid escape into tissues. Additionally, since almost all of these agents are normally cleared by the renal route, this means that fluctuations of renal function, which usually occur in septic patients, may increase or decrease their elimination rates. Conversely, lipophilic antimicrobials are less significantly affected in their pharmacokinetic behavior by the pathophysiology of sepsis. This is because they are normally distributed also within cells, and this means that retrodiffusion from the intracellular reservoir to the extracellular space may prevent antibiotic dilution whenever intravascular fluid escape into tissues. Additionally, most of these agents are cleared through the liver, whose function is often less significantly compromised during sepsis, so that their elimination rates are frequently similar to those observed in stable patients.

Accordingly, hydrophilic antimicrobials often need higher loading dosages and increased or decreased maintenance dosages in critically ill septic patients in comparison with non-critical stable patients. On the contrary, similar concentration-time profiles are observed for lipophilic agents in critically ill as well as non-critically ill patients.

5. Pharmacokinetic and pharmacodynamic parameters of antimicrobial agents

Dosage and length of the dosing interval must be determined by considering the pharmacokinetic–pharmacodynamic relationships of the antimicrobial agent. Pharmacokinetic (PK) parameters determine the concentration-time course of the antimicrobial agent. The most important PK parameters include the area under the plasma concentration time-curve ($AUC_{0-24\ h}$), the peak plasma concentration (C_{max}), and the trough concentration or the concentration prior to the next dose (C_{min}). Pharmacodynamics refers to the relationship between the antimicrobial concentration and the observed effect on the target pathogen. Crucial hereby is the in vitro susceptibility of the involved microorganism (minimal inhibitory concentration, MIC). According to the differences in dose–response relationships, antimicrobials are broadly classified in one or more of the following PK/PD categories (Table 1):

(i) Non-concentration dependent, more commonly known as time-dependent: antimicrobial effect is defined by the cumulative percentage of time over a 24 hour period that the free (or unbound) antimicrobial concentration exceeds the MIC ($f\ T_{>MIC}$). Beta-lactam antimicrobials are examples of time-dependent agents. Concentration far exceeding that of the MIC will not contribute to better killing rates [34].

(ii) Concentration-dependent: antimicrobial effect is defined by the peak concentration in a dosing interval divided by the MIC (C_{max} / MIC). Aminoglycosides and daptomycin are concentration-dependent agents. The usual target is a C_{max} / MIC that exceeds 8–10.

(iii) Concentration-dependent with time-dependence: antimicrobial effect is defined by the $AUC_{0-24\ h}$ over a 24-hour period divided by the MIC ($AUC_{0-24\ h}$ / MIC). Examples are fluoroquinolones, tigecycline, linezolid and glycopeptides [35]. Specific targets vary according to the antimicrobial.

6. Pathophysiological alterations in critically ill patients affecting antimicrobial pharmacokinetics

As already mentioned during critical illness several pathophysiological changes occur that may alter PK of drugs, mainly of the hydrophilic ones. Often multiple conditions that may influence PK are present at the same time thereby excessively complicating the prediction of adequate concentrations. Regarding antimicrobials, basically the five main issues

Table 1
Pharmacokinetic and pharmacodynamic properties of antimicrobial agents (after [39]).

	Concentration-dependent	Time-dependent	Concentration-dependent with time-dependence
Objective	Maximize concentrations	Maximize duration of exposure	Maximize amount of drug exposure
Optimal PK/PD index	C_{max}/MIC	T > MIC	$AUC_{0-24\ h}$ / MIC
Antimicrobials	Aminoglycosides	Carbapenems	Azithromycin
	Daptomycin	Cephalosporins	Clindamycin
	Fluoroquinolones	Erythromycin	Linezolid
	Ketolides	Linezolid	Tetracyclines
	Metronidazole	Clarithromycin	Fluoroquinolones
	Quinupristin/dalfopristin	Lincosamides	Aminoglycosides
		Penicillins	Quinupristin/dalfopristin
			Tigecycline
			Vancomycin

may cause alterations in PK: (1) increased Vd, (2) alterations in protein binding, (3) augmented renal clearance, (4) impaired renal clearance, and (5) hepatic dysfunction.

6.1. Increased volume of distribution (Vd)

Sepsis and particularly septic shock are characterized by vasodilatation and increased vascular permeability leading to capillary leak syndrome [36]. This capillary leak is responsible for a fluid shift from the intravascular compartment to the interstitial space [37] leading to edema formation. This third-spacing phenomenon is enhanced by oncotic pressure caused by plasma proteins leaked through the capillary leak [38]. The increased vascular capacity by vasodilatation on one hand and the loss of intravascular volume on the other hand necessitate the administration of intravenous fluids in order to maintain sufficient pressure to perfuse organ beds. Edema formation and intravenous fluid administration contribute to a vast increase in total body water substantially increasing Vd of hydrophilic antimicrobials. The clinical importance of an increased Vd is particularly relevant for those antimicrobials (beta-lactams, aminoglycosides, glycopeptides, polymyxin B) that normally have a rather low Vd. If initial loading dosages are not increased, it might take one to two days before stable serum concentrations are reached, thereby compromising clinical outcomes.

Indeed, Vd of hydrophilic antimicrobials is not only increased by edema formation and fluid administration but also by several frequently performed interventions might contribute to this, such as mechanical ventilation, extra-corporal circuits (e.g. cardiopulmonary bypass or plasma exchange), and post-surgical drainage [39]. As such, not only sepsis or septic shock but also disease severity in general may cause an increase in Vd. Specific pathologies leading to increased Vd include advanced liver disease, mediastinitis, pleural effusion, and major burn injury. Advanced liver cirrhosis may lead to an increase in extracellular compartment fluid and therefore Vd of hydrophilic antimicrobials through ascites formation and plasma expansion [40,41]. Extravasation of fluid in the pleural cavity may also trigger Vd expansion resulting in insufficient concentrations of hydrophilic antimicrobials [42]. Mediastinitis can increase Vd of antimicrobials through sequestration of plasma leading to a third spacing phenomenon [43]. Extensive burn injury incites a strong inflammatory reaction and capillary leak resulting in massive oedema formation. Direct damage of microvascular integrity by the trauma itself further promotes extravasation of plasma [44].

The relationship between increased Vd of antimicrobials and serum concentrations has been the objective of many studies. For example, in 100 surgical ICU patients with Gram-negative sepsis, Vd and serum concentrations of aminoglycosides were investigated [45]. Vd was increased by 36% to 70% leading to the need for proportionally larger loading dosages to achieve desirable target concentrations. The relationship between Vd of amikacin and severity of acute illness as assessed by the acute physiology and chronic health evaluation (APACHE) II score was investigated in 42 critically ill patients being treated for a Gram-negative sepsis [46]. Whereas the normal Vd of amikacin is about 0.25 L/kg and the mean Vd measured was 0.41 L/kg (standard deviation 0.12 L/kg). Vd correlated well with increased disease severity ($r = 0.70$; $P < 0.001$) leading to the conclusion that in critically ill patients larger loading doses of aminoglycosides are necessary to achieve target concentrations. A PK study on intravenous polymyxin B in critically ill patients demonstrated that PK was mainly dependent on total body weight, which closely related to Vd [47]. Additional Monte Carlo simulations indicated that therapeutic regimens might benefit from a loading dose.

Conversely, no major influence on Vd is expected under the aforementioned conditions for lipophilic antimicrobials. For example, no significant increase in Vd was observed for ciprofloxacin in patients with intra-abdominal sepsis, suggesting that third-space losses and fluid resuscitation had no significant influence for this lipophilic antimicrobial [48].

6.2. Protein binding

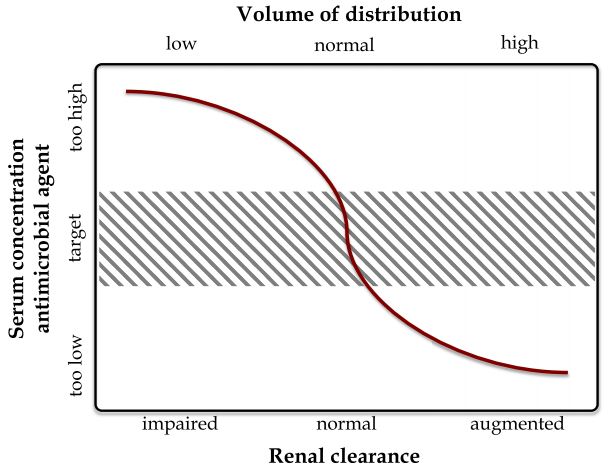
Protein binding is a relevant property of drugs as only the unbound fraction is pharmacodynamically active and can achieve drug efficacy or cause toxicity. Hypoalbuminemia frequently occurs during critical illness. More than 40% of patients admitted to ICUs have a serum albumin concentration of ≤25 g/dL at baseline [49]. Protein binding is likely to be clinically relevant when the antimicrobial agent is highly protein bound (>85–90%) and predominantly cleared by glomerular filtration, as it occurs for some hydrophilic antimicrobials like ertapenem, daptomycin, ceftriaxone and teicoplanin [50]. Lower serum protein concentrations result in greater proportions of unbound drug and may therefore temporarily result in high drug concentrations and optimal bacterial killing rates. Yet, as hypoalbuminemia is usually associated with increased Vd and drug clearance of highly protein bound hydrophilic antimicrobials, the free fraction will soon after administration be diluted over the increased total body water and more rapidly cleared. As such hypoalbuminemia may contribute to initial target concentrations but failure to maintain sufficient drug concentrations throughout the dosing interval necessitating a shorter dosing interval [50]. Roberts et al. summarized data from eight studies on antimicrobials in critically ill patients with hypoalbuminemia [50]. In all studies clearance in ICU patients was increased compared with healthy volunteers while in most studies the Vd was substantially increased. Yet, important differences between antimicrobials should be considered. For ceftriaxone, for example, clearance increased by 99% while an increment in Vd of 32% was observed [51]. For flucloxacillin, clearance and Vd increased 10% and 57% respectively [52,53]. The highest increments were observed in ertapenem with clearance and Vd raises of 462% and 624%, respectively [54]. In summary, hypoalbuminemia may result in a greater unbound drug proportion, and this means that in severe hypoalbuminemic patients higher than standard loading doses and maintenance doses may be needed for optimal exposure with highly protein bound hydrophilic antimicrobials.

6.3. Augmented renal clearance

Augmented renal clearance (ARC) refers to enhanced excretion of circulating metabolites, toxins, waste products, and drugs as compared to baseline as consequence of glomerular hyperfiltration [55]. Initially, the proposed definition of ARC uses glomerular filtration rate values 10% above the normal upper value, i.e. >160 mL/min/1.73 m^2 in men and >150 mL/min/1.73 m^2 in women [6]. More recently the cut-off was set at a glomerular filtration rate >130 mL/1.73m^2 as values above this threshold were associated with sub-therapeutic trough concentrations of beta-alctams [56]. As many hydrophilic antimicrobials are eliminated by glomerular filtration, ARC is likely to be an important PK covariate. Also, as antimicrobial clearance is generally proportionate to creatinine clearance (CL_{cr}) [6,56–58], patients at risk for subtherapeutic concentrations following ARC are becoming more recognized.

There is a variety of clinical conditions leading to ARC including sepsis, trauma, particularly burn injury, pancreatitis, autoimmune disorders, ischemia, and major surgery [12,59–61]. Often these conditions also lead to increased Vd, thereby providing an additional factor potentially contributing to insufficient antimicrobial concentrations. Fig. 2 illustrates how increased Vd and ARC both influence antimicrobial serum concentrations of hydrophilic agents. Basically, the reason for ARC can be reduced to the presence of SIRS, characterized by a reduction in systemic vascular resistance and increased cardiac output and concomitantly increased glomerular filtration rate if the kidneys are not damaged [62]. In experimental sepsis models, increments in cardiac output correlated with increased renal blood flow, while in cardiosurgical patients cardiac output was associated with creatinine clearance (CL_{cr}) [63,64]. To counteract the vasodilation fluids and eventually vasoactive agents are administered. Experimental data demonstrated that administration of crystalloids can increase CL_{cr}, and that noradrenaline is capable in enhancing cardiac output, renal blood flow, and CL_{cr} [65–67].

The way in which ARC affects antimicrobial PK/PD depends on the basis of their bacterial kill characteristics. For time-dependent antimicrobials, such as beta-lactams, it is important to maintain adequate plasma concentrations throughout the dosing interval. Therefore, such antimicrobials are extreme vulnerable for the effects of ARC. Continuous infusion of time-dependent antimicrobials has been suggested to maximize the duration of time that bacteria are exposed to adequate antimicrobial concentrations [32], especially when in the presence of multidrug resistant Gram-negative infections [68]. A recent multicentre trial demonstrated that continuous infusion of beta-lactam antibiotics in patients with severe sepsis resulted in higher plasma concentrations and some better surrogate clinical outcomes, compared with intermittent bolus infusions [69].



Legend.
Red line indicates antimicrobial serum concentration. The shaded zone indicates the target interval for the antimicrobial concentration.

Fig. 2. Schematic illustration of the influence of increased volume of distribution and augmented renal clearance on serum concentrations of hydrophilic antimicrobial agents. Red line indicates antimicrobial serum concentration. The shaded zone indicates the target interval for the antimicrobial concentration.

Conversely, C_{max} is barely affected by ARC, being mainly dependent on the Vd of a given drug and not on its clearance. Therefore the clinical relevance of ARC on conditioning adjustments of maintenance dosages of concentration-dependent antimicrobials such as aminoglycosides is rather limited as C_{max} / MIC is the most important PD index. However, it should not be overlooked that these drugs can benefit from higher loading doses in order to compensate the increased Vd. Using a standard loading dose of 25 mg/kg amikacin in 74 patients with severe sepsis or septic shock, serum peak concentrations did not reach the target C_{max} of 8 times the MIC for *Enterobacteriaceae* and *Pseudomonas aeruginosa* in 30% of study subjects [70].

For concentration-dependent antimicrobials with time-dependence such as fluoroquinolones or vancomycin, the AUC_{0-24h}/MIC is the central PK/PD index. The impact of ARC on PK of these antimicrobials may be relevant for renally cleared antimicrobials considering that for these agents $AUC_{0-24\ h}$ is inversely related to renal clearance. Standard dosages of ciprofloxacin rarely reached target concentrations in 70 critically ill patients [71]. Also for the vancomycin use in ICU patients, insufficient drug concentrations were frequently observed and linked with poor clinical outcomes [72,73]. Therapeutic drug monitoring could be used to guide drug dosing in these patients.

6.4. Reduced renal clearance

6.4.1. Acute kidney injury

Acute kidney injury (AKI) is a common complication in the ICU, particularly in the context of sepsis [74–76]. A wide range of factors can trigger the development of AKI, in particular shock due to hemorrhagic, septic or cardiogenic causes [7]. AKI is diagnosed on the basis of either an acute increase in the serum or plasma creatinine concentration or the presence of oligo-anuria.

As a large number of hydrophilic antimicrobials are renally eliminated, AKI has an important influence on antimicrobial PK. Because antimicrobial clearance corresponds with CL_{cr} [6,56–58], the impact of AKI on the antimicrobial concentrations depends on the extent that renal function is impaired. In mild-to-moderately ill patients dose adjustments for renally cleared antimicrobials might be necessary for CL_{cr} values below 50 mL/min although the need of this will vary according to the tolerability and to the safety of the antimicrobial agent.

Indeed, the type of dosage adjustments should be different for antimicrobials according to concentration-dependency or time-dependency. As a general rule, for concentration-dependent agents, like aminoglycosides and daptomycin, it is better to prolong the dosing interval while maintaining unmodified the dose amount in order to maximize C_{max}/MIC ratio. Conversely, for time-dependent agents, like beta-lactam, it is better to reduce the dose amount while maintaining unmodified the dosing interval in order to maximize t > MIC.

The impact of altered PK in case of AKI depends also on the proportion of the antimicrobial that is renally eliminated. Aminoglycosides are nearly 100% cleared by glomerular filtration. In the case of a certain reduction in CL_{cr}, there will be proportionate reduction in aminoglycoside clearance requiring a prolongation of the dosing interval [77]. Vancomycin is a glycopeptide with large Vd and clearance that correlates with CL_{cr} [6]. Factors associated with adequate early vancomycin concentrations were retrospectively investigated in 227 ICU patients [78]. A decreased CL_{cr} was found to be an independent predictor of adequate early vancomycin trough concentrations (>15 mg/mL) (OR per mg/mL increase 7.1, 95% CI 2.0–25.0; $p = 0.002$). These data insinuate that reduced renal function may partially compensate for conditions in the critically ill patient that provoke suboptimal antimicrobial concentrations. The need for dose adjustment will depend on gravity of renal dysfunction, degree of factors increasing Vd, whether a loading dose was

given, duration of therapy, and target concentration. As TDM is standard to guide vancomycin dosing, any sub- or supratherapeutic concentrations can be adjusted.

More factors than just AKI might contribute to alterations in PK observed in these patients. A careful approach to antimicrobial dose adjustment in patients with AKI is required to guarantee that predetermined PK/PD targets are still achieved to optimize clinical outcomes. The overall clinical picture should always be taken into account. As previously mentioned, in critically ill patients Vd is often enlarged for hydrophilic antimicrobials that distribute largely in extracellular water (aminoglycosides, beta-lactams, glycopeptides, colistin) and this means that they will demonstrate reduced serum concentrations when using standard loading doses. Additionally, some antimicrobial agents may present multiple elimination pathways that may compensate the decreased renal clearance in the presence of AKI, so that standard reductions of maintenance doses as recommended may potentially result in substantial underdosing in critically ill patients. For example, Pea et al. found that 400 mg of ciprofloxacin twice daily did not result in antimicrobial accumulation in critically ill patients with reduced renal function, since the drug was compensatorily eliminated by transintestinal secretion and by the hepatic pathway, and concluded that in most cases dose reductions are not necessary [79]. Likewise, in another study only 71% of renally adjusted start doses of piperacillin–tazobactam in critically ill patients with AKI achieved target concentrations [80]. Similar observations were made for cephalosporins [80] and tigecycline [81]. These results highlight the need of considering the importance of the compensatory role that multiple elimination pathways may have for some antimicrobials in critically ill patients with AKI and support the need for administering a higher loading dose to be given in the initial 24 h of treatment even in this setting [82].

6.4.2. Renal replacement therapy

In the case of life-threatening AKI, renal replacement therapy (RRT) may be required. Three types of RRT are frequently performed in ICU patients: continuous, intermittent, or an in-between approach (SLED). Continuous RRT can be applied as continuous venovenous hemofiltration (CVVH), continuous venovenous hemodialysis (CVVHD), and continuous venovenous hemodiafiltration (CVVHDF). All of these approaches are very efficient in removing hydrophilic antimicrobials, in particular those with low protein binding properties and high renal clearance [83,84]. RRT complicates predictions of antimicrobial concentrations as drug clearance may vary according to the mode of RRT, the dose of RRT delivered, filter material and surface area, and blood flow [83–86]. As such, factors that may lead to underdosing as well as overdosing are to be considered. With the data available in literature no definitive guideline for antimicrobial dosing can be proposed as study results demonstrate high interpatient variability. A useful attempt to stratified dosages of antimicrobials during CRRT according to critical factors has been made [25,84]. However, therapeutic drug monitoring seems to be the way forward to optimize antimicrobial dosing in critically ill patients requiring RRT [87].

6.5. Hepatic dysfunction

Hepatic dysfunction is caused by infection-associated with cholestasis or hepatocellular injury, ischaemic hepatitis (shock liver through hypoperfusion), hemolysis, or direct damage from hepatotoxic pharmaceuticals [31,88,89]. Hepatic dysfunction is reflected by elevated liver enzymes, bilirubin, and ammonia, or reduced synthesis of coagulant factors [31]. Hepatic impairment may sometimes lead to accumulation of hepatically metabolized antimicrobials through reduced clearance. However, liver diseases may be associated with variable and non-uniform reductions in drug-metabolizing activities. In general, the activity of the various CYP450 enzymes may be differentially affected in patients with cirrhosis, and glucuronidation is often affected to a lesser extent than CYP450-mediated reactions.

[90]. The Child–Pugh score is frequently used to guide dosage adjustment in clinical practice, despite not being validated in critically ill patients. Of note, the only antimicrobials for which dosage reduction is recommended for patients with Child–Pugh class C are metronidazole, tigecycline, and caspofungin [91–94].

Alternatively, liver failure is associated with reduced production of albumin leading to hypoproteinemia affecting Vd and protein binding. Hepatic metabolization of antibiotics such as fluoroquinolones and flucloxacillin is hampered by liver failure. Yet, it takes a reduction of at least 90% of the metabolic capacity of the liver to substantially affect drug clearance [95]. Besides intrinsic hepatic clearance, hepatic drug clearance is also influenced by hepatic blood flow. Changes in hepatic blood flow can affect drug metabolism by alterations in drug delivery to the hepatocyte. This is particularly relevant for drugs with a high extraction ratio (>0.7) [90]. Hepatic blood flow might be increased due to the hyperdynamic status that characterizes sepsis and critical illness. It is, however, unclear to which extent an increased hepatic blood flow may compensate for reduced hepatic enzyme activity due to liver disease.

For drugs such as ciprofloxacin, which are eliminated renally as well as by hepatic clearance, special attention should be given to patients in whom hepatic dysfunction occurs in the presence of acute kidney injury [31,79]. Because the impact of hepatic dysfunction on antimicrobial elimination is difficult to assess it is recommended to prescribe non-hepatically eliminated agents. This might be particularly important when accumulation of the antimicrobial might lead to hepatic toxicity, further endangering the hepatic function.

7. Variability in target attainment of antimicrobial agents and practical approach

A spectrum of pathophysiological changes and/or interventions provokes conditions that may result in either increased or decreased drug concentrations. Fig. 3 summarizes the main conditions contributing to this complex of circumstances making prediction of PK problematic. Factors that contribute to increased antimicrobial concentrations include decreased hepatic and renal failure, and regional blood flow albeit that the latter is generally a temporarily event due to shock. Factors leading to increased Vd and ARC of hydrophilic antimicrobials by which concentrations tend to decrease include inflammation, edema formation, post-surgical drainage, extra-corporal circulations, and the administrations of fluids and inotropic agents. Alteration in protein binding has two consequences. Hypoalbuminemia resulting from liver failure (e.g., cirrhosis) may lead to a greater free drug fraction and temporarily higher exposure. However, cirrhotic patients often experience ascites adding to an increase in Vd of hydrophilic antimicrobials. Also, and more frequent in critically ill patients, hypoalbuminemia might result from capillary leak syndrome. Serum proteins leaked into the interstitial space enhance edema formation and as such Vd.

One or more of these factors may be present in various degrees of seriousness according to the severity of acute illness that – on its turn – may vary in time (i.e. on a daily or even an hourly basis). As a consequence intra- and inter-patient variability of target attainment in critically ill patients is substantial and clinically relevant as has been demonstrated with beta-lactams and vancomycin [80,96]. While evaluating target attainments of antimicrobials one should consider the threshold chosen. In a recent multinational PK point-prevalence study concentrations of beta-lactams were evaluated with as main PK/PD target free concentrations above the MIC of the pathogen at both 50% and 100% of the dosing interval [97]. The study revealed that 21% of patients did not achieve the minimum conservative PK/PD target of >50% T > MIC. In order to achieve adequate bacterial killing, concentrations should exceed 4 × MIC for 50% of the dosing interval; a target that was only achieved by 49% of patients. The optimal scenario in which antimicrobial concentrations exceeded 4 × MIC for the total duration of the dosing interval was observed in only 35% of the ICU patients.

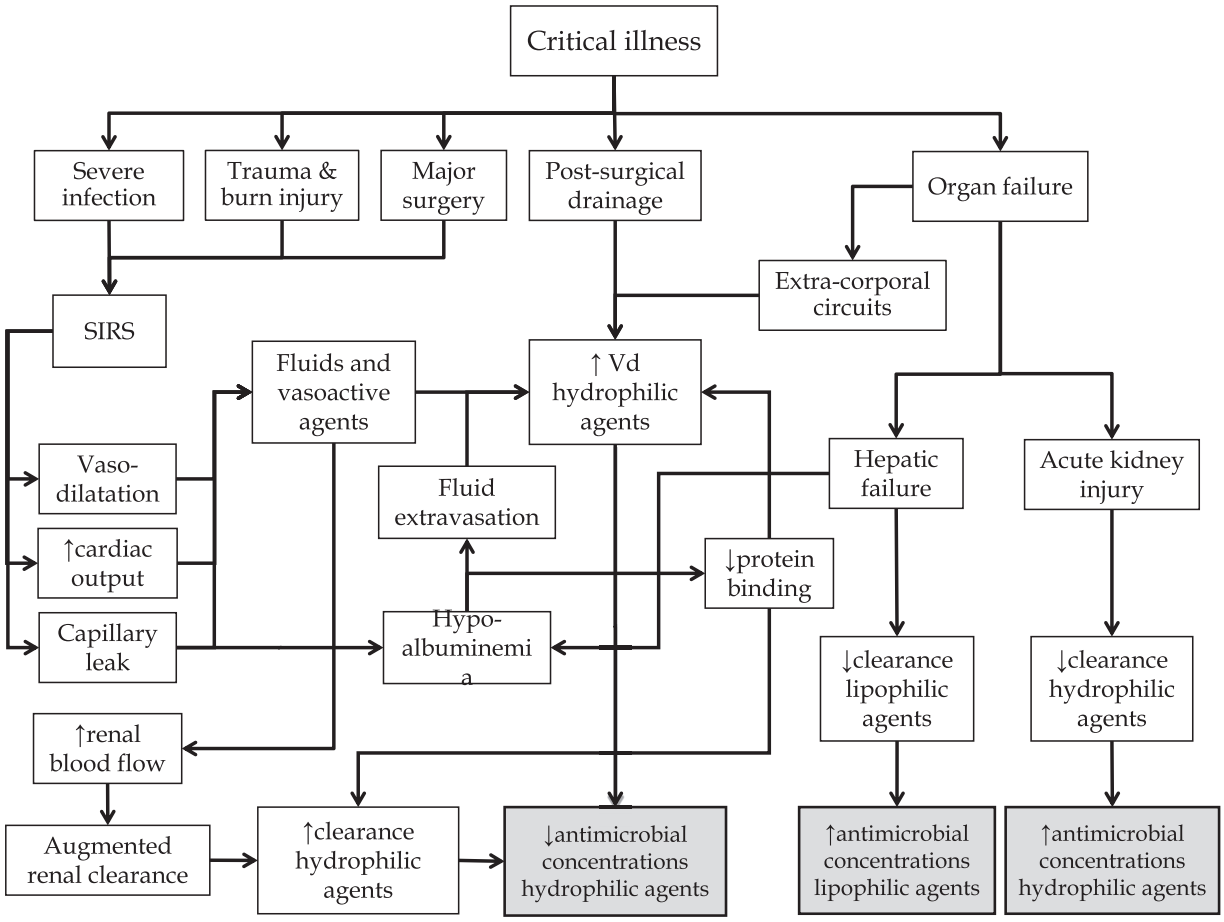


Fig. 3. Review of pathophysiological alterations during critical illness and their potential effect on pharmacokinetics of antimicrobial agents. SIRS, systemic inflammatory response syndrome; Vd, volume of distribution.

In order to deal with the high interpatient variability a patient-tailored approach by means of TDM has been proposed. Historically, TDM has been used for antimicrobials with a rather narrow therapeutic window and a substantial risk of toxicity (e.g. aminoglycosides, vancomycin), while it was considered less useful for agents with a broad therapeutic index such as beta-lactams [98]. At least theoretically TDM offers a way to counter the high inter-patient PK variability. The rationale for this is that TDM of antimicrobials may allow targeting drug exposure in all of the patients, irrespective of their underlying conditions, to the same value which is expected with the standard licensed dosages in the healthy volunteers. This may maximize the likelihood of clinical response and minimize that of adverse events. Yet, despite the successfully implementation of a beta-lactam TDM-program in ICU patients [87], several issues remain. First, clinical advantage remains unproven. Second, the technical requirements and expertise are not widely available. Third, the possibility of TDM does not solve the question of the most optimal PK/PD target. Fourth, when the predefined target is missed it remains unclear how to titrate the dose. Finally, turnaround times of TDM must be reduced. In the proof-of-concept paper by Roberts et al. beta-lactam concentrations were available within 12 h of sampling [87]. This may be advanced from a laboratory perspective but it is probably too long from the clinical viewpoint, especially in first 48 h in which prompt and adequate antimicrobial therapy is crucial to optimize the odds of survival [9,22]. Due to the high turn-around time, TDM may well run behind the clinical scenario. Because the first two days represent a critical time in anti-infective management it is of utmost importance to achieve target concentrations in a timely manner. It can be questioned if TDM is the best approach to achieve PK targets at earliest convenience. To increase the likelihood of early target attainment, PK models can be developed to steer antimicrobial dosing in the initial phase of therapy. These models can take into account status of mechanical ventilation, diagnostic category, and glomerular filtration [99–101]. However, also here problems arise. Renal function is pivotal in such models and often estimated by either Cockroft–Gault or modified diet in renal disease formula. These formulas are based on single serum creatinine concentrations and only validated in patients with stable renal function. In the context of critical illness and acute kidney injury however, it might take hours or days for creatinine concentrations to reach steady state. Moreover, other factors affecting PK such as the influence of capillary leak on Vd (e.g. in septic shock or burn trauma) are much more difficult to estimate thereby hampering the development of PK models that are valid for all expressions of critical illness.

8. Conclusion

Dosing of antimicrobials during sepsis or critical illness in general is problematic as antimicrobial concentrations are subject to alterations. Overall, the risk of suboptimal concentrations is higher than the risk of adverse effects due to overdosing, especially for hydrophilic compounds. Patients are at risk for overdosing in the case of fulminant liver failure or strongly impaired renal function not covered by renal replacement therapy. But when starting antimicrobial therapy even in the event of pending toxicity due to inefficient clearance, the deleterious effects of overexposing will be blunted by conditions generating a dilution of the drug (increased Vd). From the available data in critically ill patients it is clear that underdosing is much more frequent than

overdosing. Inadequate drug concentrations are clinically relevant as they lead to inefficient microbial killing and hence, compromise clinical outcomes. In addition, suboptimal antimicrobial concentrations further trigger the development of multidrug resistance, which on its turn further complicates antimicrobial therapy through reduced odds of empiric appropriate treatment. This suggests antibiotic TDM will become more commonly used to assist optimal dosing within the ICU.

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