REVIEW ARTICLE

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Antimicrobial Therapy in Critically Ill Patients

A Review of Pathophysiological Conditions Responsible for Altered Disposition and Pharmacokinetic Variability

Federico Pea,[1] *Pierluigi Viale*[2] and *Mario Furlanut*[1]

1 Department of Experimental and Clinical Pathology and Medicine, Medical School, Institute of Clinical Pharmacology and Toxicology, University of Udine, Udine, Italy
2 Department of Medical and Morphological Research, Medical School, Clinic of Infectious Diseases, University of Udine, Udine, Italy

Contents

Abstract . . . 1009
1. General Principles for Appropriate Prescription of Antimicrobials in Critically Ill Patients . . . 1010
2. General Intrinsic Characteristics of Antimicrobials . . . 1013
3. Influence of Different Pathophysiological Mechanisms in Altering Disposition of Antimicrobials in Critically Ill Patients . . . 1014
4. Pathophysiological Conditions Altering Pharmacokinetics of Antimicrobials in Critically Ill Patients . . . 1015
   4.1 Causes of Increased Volume of Distribution . . . 1015
      4.1.1 Oedema . . . 1015
      4.1.2 Fluid Therapy or Parenteral Nutrition . . . 1019
      4.1.3 Pleural Effusion . . . 1020
      4.1.4 Ascites and Peritoneal Exudate . . . 1020
      4.1.5 Mediastinitis . . . 1021
      4.1.6 Indwelling Post-surgical Drainages . . . 1021
      4.1.7 Hypoalbuminaemia . . . 1021
   4.2 Causes of Enhanced Renal Clearance . . . 1022
      4.2.1 Burns . . . 1022
      4.2.2 Hyperdynamics . . . 1023
      4.2.3 Haemodynamically Active Drugs . . . 1024
      4.2.4 Acute Leukaemia . . . 1025
      4.2.5 Drug Abuse . . . 1026
   4.3 Causes of Reduced Renal Clearance . . . 1026
      4.3.1 Renal Failure . . . 1026
      4.3.2 Muscle Wastage and Long-Term Bedridden Patients . . . 1027
5. The Importance of a Multidisciplinary Team in Tailoring Antimicrobial Therapy in Critically Ill Patients . . . 1027
6. Conclusion . . . 1029

Abstract

Antimicrobials are among the most important and commonly prescribed drugs in the management of critically ill patients. Selecting the appropriate antimicrobial at the commencement of therapy, both in terms of spectrum of activity and dose

and frequency of administration according to concentration or time dependency, is mandatory in this setting. Despite appropriate standard dosage regimens, failure of the antimicrobial treatment may occur because of the inability of the antimicrobial to achieve adequate concentrations at the infection site through alterations in its pharmacokinetics due to underlying pathophysiological conditions.

According to the intrinsic chemicophysical properties of antimicrobials, hydrophilic antimicrobials (β-lactams, aminoglycosides, glycopeptides) have to be considered at much higher risk of inter- and intraindividual pharmacokinetic variations than lipophilic antimicrobials (macrolides, fluoroquinolones, tetracyclines, chloramphenicol, rifampicin [rifampin]) in critically ill patients, with significant frequent fluctuations of plasma concentrations that may require significant dosage adjustments. For example, underexposure may occur because of increased volume of distribution (as a result of oedema in sepsis and trauma, pleural effusion, ascites, mediastinitis, fluid therapy or indwelling post-surgical drainage) and/or enhanced renal clearance (as a result of burns, drug abuse, hyperdynamic conditions during sepsis, acute leukaemia or use of haemodynamically active drugs). On the other hand, overexposure may occur because of a drop in renal clearance caused by renal impairment. Care with all these factors whenever choosing an antimicrobial may substantially improve the outcome of antimicrobial therapy in critically ill patients. However, since these situations may often coexist in the same patient and pharmacokinetic variability may be unpredictable, the antimicrobial policy may further benefit from real-time application of therapeutic drug monitoring, since this practice, by tailoring exposure to the individual patient, may consequently be helpful both in improving the outcome of antimicrobial therapy and in containing the spread of resistance in the hospital setting.

1. General Principles for Appropriate Prescription of Antimicrobials in Critically Ill Patients

Critically ill patients, especially when admitted to intensive care units (ICUs), are at very high risk of developing severe nosocomial infections, with incidence rates about 5- to 10-fold higher than in general medical wards.[1,2] In the EPIC (European Prevalence of Infection in Intensive Care) study, Vincent et al.[1] reported a prevalence for nosocomial infections in ICUs of 20.6%, about half of which (46.9%) were pneumonia, while other studies have quoted incidence rates ranging between 9% and 37%, these differences being mainly related to different inclusion criteria of the studied populations.[3]

Antimicrobials are consistently among the most important and commonly prescribed drugs in the management of ICU patients,[4] and appropriate policies for their wise use should be accurately defined in these settings.[5]

It is worth noting that the inappropriate use of antimicrobials may cause therapeutic failure or delayed clinical response in the individual patient, and at the same time antimicrobial exposure may contribute towards promoting the colonisation and spread of resistant pathogens in the ICU.[6]

Looking at the recent past, it should not be overlooked that the selective antimicrobial pressure caused by the extensive use of a given class of antimicrobials was often chronologically correlated with the proliferation of resistant strains. Historically, this occurred in the 1960s with methicillin-resistant *Staphylococcus aureus*, in the 1980s with β-lactamase-producing Gram-negative bacteria,[7] in the early 1990s with vancomycin-resistant enterococci, in the late 1990s with glycopeptide intermedi-

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ate sensitive *S. aureus*[8] and fluoroquinolone-resistant *Pseudomonas aeruginosa*,[9] concluding with the recent isolation of a totally vancomycin-resistant strain of *S. aureus*.[10,11]

Among the putative causes of failure of antimicrobial therapy, inadequate spectrum of activity of the selected antimicrobials, presence of host immunosuppression, severity of underlying diseases, withdrawal due to adverse effects, inappropriate length of therapy, emergence of breakthrough resistance or development of superinfections may be relevant.

Selecting the appropriate antimicrobial at the commencement of therapy is certainly mandatory, since an inappropriate initial choice may be responsible for higher therapeutic failure and higher mortality rates in the ICU setting, as definitely demonstrated in several studies.[12-15] Therefore, with the intent of ensuring broad-spectrum empirical antimicrobial therapies, several guidelines have been developed according to pathophysiological and epidemiological features.[16-19] However, it has not to be overlooked that, once culture results become available, anti-infective therapies must be narrowed in order to preserve the most effective drugs (i.e. carbapenems, fluoroquinolones) and, at the same time, avoid adverse effects and contain pharmaceutical expenditure.[20,21] Moreover, different methods for implementing antimicrobial control (e.g. periodic cycling of the empirically used antimicrobials,[22-28] restriction of formulary,[29] antimicrobial order forms or stop order forms,[30] computerised systems,[31]) have been advocated, even if conflicting opinions still exist in the literature.

Although selecting the appropriate antimicrobial in terms of spectrum of activity is certainly the mainstay of antimicrobial therapy in critically ill patients, the consistent choice of correct dosage regimen (in terms of both dose and frequency of administration) has definitely been shown in the last 10 years to be at least of the same importance in ensuring successful clinical cure and microbiological eradication.[32-37] The dose and length of dosing interval should be chosen by taking into account the pharmacokinetic/pharmacodynamic relationships of each class of antimicrobial. This recommendation is drawn on the basis of the integration between the *in vitro* susceptibility of the involved aetiological organism (minimum inhibitory concentration [MIC]) and the *in vivo* pharmacokinetic indicators of quantitative and qualitative drug exposure (area under the plasma concentration-time curve [AUC], peak plasma concentration [C_{max}] and minimum plasma concentration [C_{min}]). Such strategy helps in preventing the colonisation and spread of resistant strains.

Three major pharmacodynamic determinants of antimicrobial efficacy have been identified: the duration of time the concentration exceeds the MIC (t>MIC), C_{max}/MIC ratio and the AUC/MIC ratio. According to the different relative importance of these determinants, antimicrobial activity may be defined as time-dependent or concentration-dependent. Time-dependent antimicrobials whose efficacy is mainly related to t>MIC are β-lactams, glycopeptides and oxazolidinones. Particularly, it has been shown that t>MIC must be at least 50% of the dosage interval to ensure standard efficacy with these antimicrobials,[37,38] whereas t>MIC of 100% of the dosage interval should be ensured for optimal exposure in immunocompromised patients. Indeed, a further improvement in efficacy of time-dependent antimicrobials has been observed when concentrations 4- to 5-fold greater than the MIC are achieved,[39] whereas no further benefit will be obtained with higher levels. Additionally, all of these antimicrobials (with the notable exception of the carbapenems) exhibit valid post-antimicrobial effect (PAE) against only Gram-positive microorganisms.[40] Therefore, very low trough levels should be avoided since bacteria rapidly recover and start regrowing as soon as concentrations fall below the MIC. As a consequence, in order to avoid drug-free intervals, the shorter the terminal elimination half-life ($t_{1/2}\beta$) of the drug, the more frequent the dose fractioning (from two to six times per day) must be, and in some situations even the application of continuous intravenous infusion may be beneficial in improving efficacy. In fact, under the same total daily dosage, continuous intravenous infusion may represent the best mode of administering time-

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dependent antimicrobials by ensuring the highest steady-state concentration.[39,41,42]

Concentration-dependent antimicrobials whose efficacy is mainly related to the C_{max}/MIC and AUC/MIC ratios are fluoroquinolones and aminoglycosides. Forrest et al.[43] were among the first to demonstrate the usefulness of these pharmacokinetic/pharmacodynamic parameters for fluoroquinolone efficacy, showing that in patients treated with ciprofloxacin for lower respiratory tract infections the probability of both clinical cure and bacterial eradication achieved good levels when the AUC/MIC ratio was at least 100–125. More recently, it has been postulated that whereas this threshold has to be considered mandatory against Gram-negative pathogens,[33,44] an AUC/MIC ratio of 30–40 might be sufficient against Gram-positive pathogens.[45,46] Moreover, several studies showed that a C_{max}/MIC ratio of 10–12 may ensure clinical cure and may prevent the spreading of resistance with these antimicrobials.[47-50] Additionally, most aminoglycosides and fluoroquinolones show valid PAE against both Gram-positive and Gram-negative microorganisms,[40,51] so that sub-MIC trough levels at the end of the dosage interval may be allowed.[52] On this basis, the best dosage regimen for concentration-dependent antimicrobials has to be considered the less fractioned one according to the toxicity pattern and length of $t_{1/2}\beta$ of each antimicrobial. Once-daily dosing should be preferred whenever possible,[53] but if this is inapplicable due to either toxicity or short $t_{1/2}\beta$, twice-daily dosing may be helpful in enabling sufficiently high plasma peaks while ensuring the same total daily exposure.

In applying these pharmacokinetic/pharmacodynamic concepts, it is important that only the unbound fraction of the drug should be considered as it is the only one microbiologically active and able to pass capillary endothelium and diffuse in tissues.

Despite the application of appropriate standard dosage regimens, failure of the antimicrobial treatment in critically ill patients may further occur because of impairment of immunological function or because of the inability of the antimicrobial to achieve adequate concentrations at the infection site, this being a frequently neglected concern in the recent past.[33] It is well known that underexposure in difficult-to-access sites (i.e. CNS or eye) may occur because of poor tissue penetration during systemic administration of standard dosages of antimicrobial. However, more importantly, in critically ill patients underexposure may also occur in unrestricted accessible sites because of high inoculum, for example, as sometimes occur in pneumonia or always in endocarditis, and/or because of altered pharmacokinetics of antimicrobials due to underlying pathophysiological conditions.

It should not be overlooked, with the exception of bloodstream infections in which microorganisms are located in the plasma compartment, that the actual compartment of bacterial infection is, in most patients, the extracellular fluid space. Therefore, to effectively treat these infections, physicians must be aware of ensuring adequate concentrations not only in plasma, but also in the extracellular tissue compartment. Indeed, Craig[37] stated that plasma concentrations of a drug may be predictive of interstitial tissue fluid concentrations, since an equilibrium between the two environments is usually achieved. Drug concentrations in plasma (or serum) are much better predictors of interstitial fluid levels than are tissue homogenate concentrations in which the interstitial, intracellular and vascular compartments are mixed together.[37]

However, a discrepancy between plasma and interstitial fluid levels of unbound drug may occur in critically ill patients, since distribution of antimicrobials in tissue may be substantially impaired.[54] On this basis, several methods have been proposed with the intent of studying target site drug distribution in antimicrobial chemotherapy,[54] among which microdialysis may be considered one of the most promising techniques in detecting interstitial fluid levels of antimicrobials, especially in soft tissues, in many different clinical settings.[54]

Therefore, whenever available, data concerning interstitial fluid concentrations may perhaps be more informative, but if these are lacking, plasma concentration data should be considered helpful.

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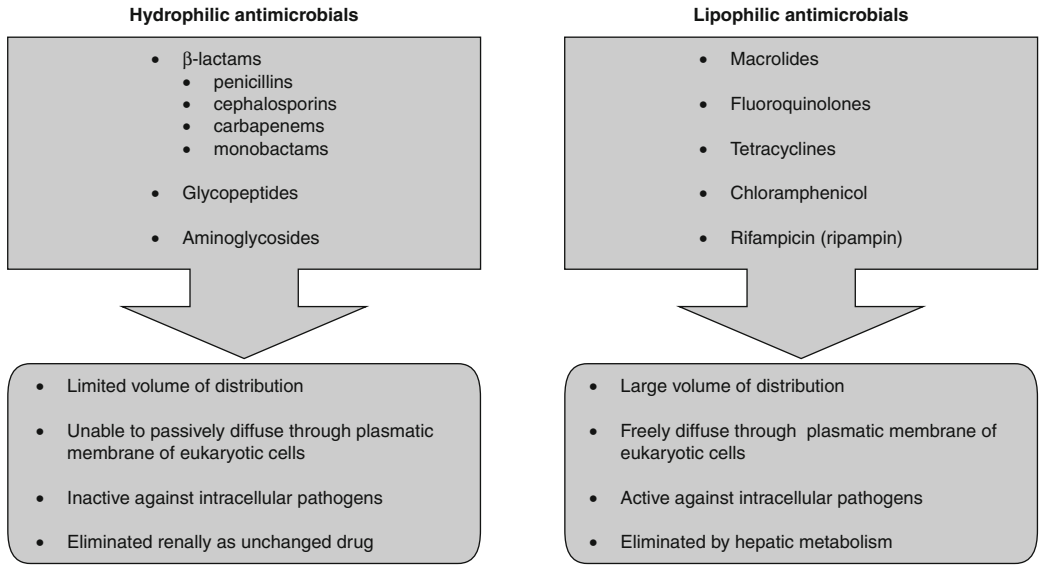

Fig. 1. Classification of antimicrobials according to their solubility and pharmacokinetic/pharmacodynamic properties.

Of note, according to the intrinsic characteristics of antimicrobials, drug disposition in the body may be affected, to a variable extent, by the different underlying diseases.

2. General Intrinsic Characteristics of Antimicrobials

Chemicophysical properties, molecular weight and degree of plasma protein binding are among the most important intrinsic characteristics conditioning disposition of a given drug in the body.

Antimicrobials may be divided into two major groups according to their solubility: hydrophilic and lipophilic (figure 1). Because of their inability to passively diffuse through the plasmatic membrane of eukaryotic cells, hydrophilic antimicrobials (e.g. β-lactams, glycopeptides and aminoglycosides) are characterised, from a pharmacodynamic point of view, by their inactivity against intracellular pathogens (i.e. *Legionella pneumophila*, *Chlamydia pneumoniae*) and, from a pharmacokinetic point of view, either by volume of distribution (V_d) limited at the extracellular space or by major renal elimination as unchanged drug.

Conversely, by freely crossing the plasmatic membrane of eukaryotic cells, lipophilic antimicrobials (e.g. macrolides, most fluoroquinolones, tetracyclines, chloramphenicol and rifampicin [rifampin]) are characterised, from a pharmacodynamic point of view, by their activity against intracellular pathogens and, from a pharmacokinetic point of view, by intracellular penetration with wide distribution and, whenever presenting low enough molecular weight, with extensive diffusion through anatomical barriers (for example the blood-brain barrier).[55] On the other hand, due to their lipophilic nature they often have to be metabolised through different pathways, mainly by the liver, to eliminate them from the body. Obviously, there are some notable exceptions to these rules. For example, levofloxacin and gatifloxacin, two moderately lipophilic fluoroquinolones, are mainly renally excreted as antimicrobially active unchanged drugs (>75%),[56,57] while azithromycin, a highly lipophilic macrolide, is not metabolised but almost completely eliminated unchanged in the faeces through biliary excretion.[58]

According to hydrophilicity or lipophilicity, the pharmacokinetics of antimicrobials may be affected,

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to a different extent, by the various underlying diseases occurring in critically ill patients.

3. Influence of Different Pathophysiological Mechanisms in Altering Disposition of Antimicrobials in Critically Ill Patients

Variations occurring in the extracellular fluid content and/or in renal or liver function may be considered the most relevant and frequent pathophysiological mechanisms possibly affecting drug disposition in critically ill patients. Compared with healthy volunteers or non-critically ill patients, some of these situations may promote significant changes of drug disposition in individual patients even in a brief period of hours by altering distribution and/or elimination processes.

Of note, hydrophilic and renally excreted moderately lipophilic antimicrobials must be considered at much higher risk of presenting substantial daily fluctuations of plasma concentrations that may require repeated subsequent dosage adjustments in individual patients. For example, regarding V_d, it is well known that the presence of extensive fluid extravasation, i.e. ascites or pleural effusions, by causing dilution in the extracellular compartment – the most frequent location site of infection – may lower antimicrobial concentrations in the body. However, according to hydrophilicity or lipophilicity, the net effect of dilution might be substantial or negligible, respectively. In fact, since hydrophilic antimicrobials exhibit V_d limited at the extracellular space (<0.3–0.4 L/kg for most aminoglycosides, β-lactams and glycopeptides), their plasma and interstitial concentrations may dramatically drop because of substantial fluid extravasation (3L).[59,60] On the other hand, for lipophilic antimicrobials presenting larger volumes of distribution (>1 L/kg for most fluoroquinolones or macrolides), the dilution of interstitial fluids caused by the presence of such extra volume will be less relevant as a consequence of higher intra-/extracellular concentration ratios.[60]

Likewise, significant daily fluctuations of plasma and extracellular concentrations of hydrophilic and moderately lipophilic renally excreted antimicrobials may occur because of dynamic changes in renal function, an event frequently occurring in critically ill patients.

Conversely, the disposition of most lipophilic antimicrobials, although only minimally or moderately affected by changes in renal function, may vary significantly according to the degree of hepatic function.[61] However, significant reduction in the elimination of most lipophilic antimicrobials should occur only in the presence of advanced liver diseases (i.e. severe cirrhosis, acute hepatitis) conspicuously impairing hepatic blood flow and/or metabolic activity.[61] On the other hand, daily fluctuations of liver function are uncommon even in critically ill patients and therefore they should not be considered a major cause of daily fluctuations of concentrations during therapy with lipophilic antimicrobials. Liver transplant patients during the first 2 or 3 weeks post-transplantation may obviously represent a notable exception to this rule.[62]

In summary, generally speaking this means that in critically ill patients hydrophilic and moderately lipophilic antimicrobials, being at higher risk of daily pharmacokinetic variations, should be more closely monitored and their dosages should be streamlined according to the underlying diseases in order to prevent under- or overexposure. Consistent with this, when searching PubMed for data to review the modifications in pharmacokinetics of antimicrobials occurring in critically ill patients we found that most findings referred to these groups of antimicrobials, whereas data regarding highly lipophilic antimicrobials were generally lacking.

Accordingly, most of the information on pharmacokinetic changes of antimicrobials in critically ill patients reported in this review concern third- or fourth-generation cephalosporins, carbapenems, penicillins, monobactams, glycopeptides, aminoglycosides, ciprofloxacin and levofloxacin, whereas very few data, if any, concerning macrolides, tetracyclines, chloramphenicol, rifampicin are reported. Data on this topic concerning new antimicrobials such as ertapenem, linezolid, gemifloxacin, gatifloxacin and moxifloxacin are also presently lacking.

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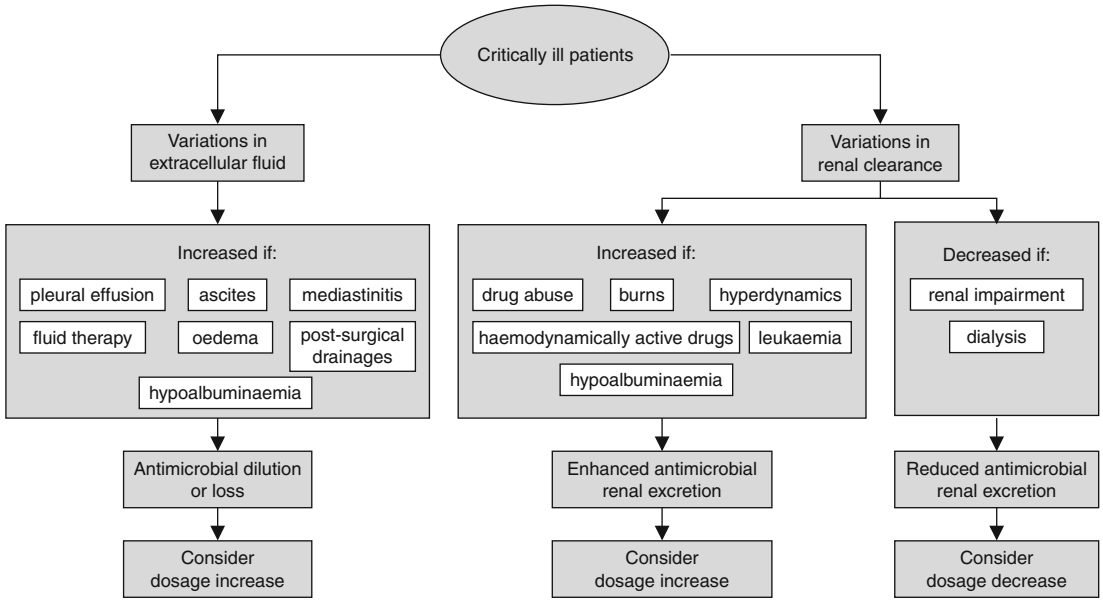

Fig. 2. Pathophysiological or iatrogenic conditions affecting the distribution and elimination of antimicrobials, and clinical recommendations in such conditions.

4. Pathophysiological Conditions Altering Pharmacokinetics of Antimicrobials in Critically Ill Patients

Critically ill patients often present with several peculiar pathophysiological or iatrogenic conditions, which may substantially affect both distribution and elimination of antimicrobials (figure 2, table I); taking this into account may be critical in ensuring a successful outcome of antimicrobial therapy.

For further clarification of pharmacokinetic drug-drug interactions in the ICU setting, readers are referred to our previously published review.[98]

4.1 Causes of Increased Volume of Distribution

Several pathophysiological situations through increasing the V_d may cause antimicrobial dilution (especially for hydrophilic antimicrobials) in plasma and extracellular fluids, so that an increase in dosage should be considered with the intent of ensuring optimal care. This may be especially true for concentration-dependent antimicrobials with a small V_d (especially aminoglycosides), which require loading doses (LDs) to be administered at the commencement of therapy, since LD is directly proportional to the drug V_d ($LD = C_{target} \times V_d$), where C_{target} is the target concentration,[99] and a low peak level due to high V_d might result in more frequent development of resistance. However, it should not be overlooked that for antimicrobials with a low V_d the presence of such extra volume in the interstitial fluid compartment may substantially increase total bodyweight ('weight gain') thus potentially also resulting in the need for higher maintenance dosages.

4.1.1 Oedema

The *per se* influence of oedema on the pharmacokinetics of drugs has rarely been accurately assessed.[59] However, the oedematous status, regardless of the underlying pathogenetic mechanism, may certainly play a major role in altering distribution of drugs, especially of those antimicrobials showing limited extracellular distribution, namely hydrophilic antimicrobials. Among the multiple causes of oedema, sepsis and trauma are the two that most frequently expand the extracellular fluids of critically ill patients. Both the endothelial damage leading

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Table I. Factors affecting pharmacokinetics of antimicrobials in critically ill patients

Study	Pathophysiological or iatrogenic situation	Study population	Antimicrobial	Mechanism(s)	Pharmacokinetic effect	Comment/clinical significance
Dorman et al.[63]a	Oedema	52 septic surgical patients	Gentamicin or tobramycin	Capillary leakage; hypoalbuminaemia	↑ V_d; ↓ C_{max}	↑ Loading doses needed
Brunner et al.[66]	Oedema	6 postsurgical patients vs 6 controls	Piperacillin/tazobactam	Capillary leakage	↓ AUC in muscle and subcutis	Inadequate t>MIC for high-MIC strains
Joukhadar et al.[67]	Oedema	6 septic patients vs 6 controls	Piperacillin	Capillary leakage	↓ AUC in muscle and subcutis	↑ Doses needed
Joukhadar et al.[68]	Oedema	12 septic patients vs 6 controls	Piperacillin	Capillary leakage	↓ C_{max} and AUC in muscle	↑ Doses needed
Gomez et al.[69]	Oedema	15 critically ill patients	Ceftazidime	Capillary leakage	↓ C_{min}	Standard doses insufficient
Hanes et al.[70]	Oedema	31 trauma patients	Ceftazidime – intermittent IV or continuous IV infusion	Capillary leakage	↑ V_d	Continuous IV infusion regimen suggested
McKindley et al.[71]	Oedema	20 trauma patients	Aztreonam or imipenem	Capillary leakage	↑ V_d	Standard initial doses insufficient
Botha et al.[72]	Fluid therapy	1 trauma patient	Amikacin	Extracellular compartment expansion	↑ V_d	Frequent TDM required
Gous et al.[73]	Fluid therapy	Critically ill infants	Vancomycin	Extracellular compartment expansion	↑ V_d	Frequent TDM required
Ronchera-Oms et al.[74]	Parenteral nutrition	86 critically ill patients	Gentamicin	Extracellular compartment expansion	↑ V_d; ↓ C_{max}	↑ Doses needed
Etzel et al.[75]	Pleural effusion	260 patients with pleural effusion vs 1049 patients without pleural effusion	Gentamicin or tobramycin	Extracellular compartment expansion	↑ V_d; ↓ C_{max}	↑ Doses needed
Aldaz et al.[76]	Ascites	154 cancer patients	Vancomycin	Extracellular compartment expansion	↑ V_d	Dosage adjustment needed
Buijk et al.[77]	Peritoneal exudate and/or drainages	18 patients with intra-abdominal infection	Ceftazidime – intermittent IV or continuous IV infusion	Extracellular compartment expansion	↑ V_d	↑ Doses needed
Romano et al.[78]	Hypoalbuminaemia	121 oncohaematological patients	Amikacin	↓ Plasma oncotic pressure	↑ V_d	↑ Doses needed
Pea et al.[79]	Hypoalbuminaemia	1 transplant patient	Teicoplanin	↓ Plasma oncotic pressure; ↑ free drug	↑ V_d; ↑ CL	↑ Doses needed
Sanchez et al.[80]	Hypoalbuminaemia plus fluid therapy	21 critically ill children	Teicoplanin	↓ Plasma oncotic pressure; ↑ free drug	↓ C_{min}	↑ Doses needed

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Table I. Contd

Study	Pathophysiological or iatrogenic situation	Study population	Antimicrobial	Mechanism(s)	Pharmacokinetic effect	Comment/clinical significance
Joynt et al.[81]	Hypoalbuminaemia plus haemodynamically active drugs	10 septic patients	Ceftriaxone	↓ Plasma oncotic pressure; ↑ free drug	↑ V_d; ↑ CL; ↓ C_{min}	↑ Doses or continuous infusion needed
Mimoz et al.[82]	Hypoalbuminaemia	11 postsurgical patients vs 11 controls	Ceftriaxone	↓ Plasma oncotic pressure; ↑ free drug	↑ V_d	Enhanced efficacy
Bonapace et al.[83]	Burns	12 burn patients	Cefepime	Weeping in exudates; ↑ in cardiac output	↑ V_d; ↑ CL	↑ Doses might be needed
Sampol et al.[84]	Burns	6 burn patients	Cefepime	Weeping in exudates	↑ V_d; ↔CL	Use standard dosage
Tang et al.[65]	Hyperdynamics	77 critically ill patients vs 27 controls	Gentamicin	↑ Cardiac output	↑ CL	Correlation with CL_{CR}
Hanes et al.[70]	Hyperdynamics	31 trauma patients	Ceftazidime – intermittent IV or continuous IV infusion	↑ Cardiac output	↑ CL	Continuous IV infusion regimen suggested
Pea et al.[85]	Hyperdynamics plus haemodynamically active drugs	10 ventilator-associated pneumonia patients	Levofloxacin	↑ Cardiac output; ↑ in glomerular filtration rate	↑ CL	↑ Doses needed
Lipman et al.[86]	Hyperdynamics	10 septic patients	Cefepime	↑ Glomerular filtration rate	↑ CL	↑ Doses needed
Lipman et al.[87]	Hyperdynamics	25 critically ill patients	Cefepime or cefpirome	↑ Glomerular filtration rate	↑ CL	↑ Doses needed or apply continuous IV infusion
Pea et al.[88]	Haemodynamically active drugs	18 cardiosurgical patients	Vancomycin	↑ Glomerular filtration rate and tubular secretion	↑ CL	TDM strongly recommended
Fernandez de Gatta et al.[89]b	Leukaemia	31 oncohaematological patients vs 9 controls	Vancomycin	↑ Glomerular filtration rate and/or tubular secretion	↑ CL	↑ Doses needed
Pea et al.[92]	Leukaemia	33 leukaemic patients	Teicoplanin	Hypoalbuminaemia, ↑ in renal blood flow	↑ V_d; ↑ CL	↑ Doses needed
King et al.[93]c	Drug abuse	18 drug abusers	Gentamicin	↑ Glomerular filtration rate	↑ CL	↑ Doses needed
Lugo and Castaneda-Hernandez[96]	Renal failure	30 critically ill patients	Amikacin	↓ Glomerular filtration rate	↓ CL	↓ Doses needed
Pea et al.[97]	Muscle wastage	1 spinal cord injury patient	Vancomycin	Overestimation of glomerular filtration rate	Overestimation of CL	Measurement of CL_{CR} and TDM strongly recommended

a Other studies include Zaske et al.[64] and Tang et al.[65].

b Other studies include Le Normand et al.[90] and Chang.[91].

c Other studies include Rybak et al.[94,95].

AUC = area under the plasma concentration-time curve; **CL** = total body clearance; **CL_{CR}** = creatinine clearance; **C_{max}** = peak plasma concentration; **C_{min}** = minimum plasma concentration; **IV** = intravenous; **TDM** = therapeutic drug monitoring; **t>MIC** = duration of time the concentration exceeds minimum inhibitory concentration; **V_d** = volume of distribution; ↑ indicates increase; ↓ indicates decrease; ↔ indicates no change.

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to increased capillary permeability[100,101] and the conspicuous reduction of oncotic pressure due to severe hypoalbuminaemia (<1.5 mg/dL)[59] may promote substantial fluid extravasation responsible for the so-called 'third spacing' phenomenon.

Several studies documented that oedematous status, by increasing V_d and lowering antimicrobial concentrations, could cause clinical failure of antimicrobial therapy in sepsis and/or trauma. Interestingly, aminoglycosides were among the most studied drugs,[64,102-114] consistently showing a drop in peak plasma concentrations, possibly causing impairment of their concentration-dependent bactericidal efficacy. Two examples are outlined here; for an exhaustive review on increased V_d of aminoglycosides in patients with sepsis the readers are referred to the work of De Paepe et al.[115]

Dorman et al.[63] assessed the initial peak plasma concentrations achievable after a 3 mg/kg loading dose (based on an adjusted bodyweight defined as the sum of ideal bodyweight plus half the difference between actual and ideal bodyweight) of aminoglycosides (gentamicin or tobramycin) in 52 critically ill surgical patients with life-threatening Gram-negative infections. Based on previously published data, this initial loading dose was estimated to produce a peak level of 8.3 mg/L. Indeed, due to a 1.34-fold increase in V_d, the target peak plasma concentration of ≥8.3 mg/L was not achieved in about half of the patients, and in 15.3% of patients the peak plasma concentration was even lower than 5 mg/L. These findings lead the investigators to conclude that greater loading doses (at least 3.7 mg/kg) are required to achieve valid peak plasma concentrations in critically ill surgical patients. Likewise, a 1.66-fold increase of V_d of gentamicin due to hyperdynamic conditions causing increased cardiac output and low systemic vascular resistance occurred in critically ill septic surgical patients.[65]

Also, the V_d of several β-lactams was shown to increase because of oedema in critically ill patients.[60]

Brunner et al.[66] examined, by means of microdialysis, the influences of cardiac surgery and extracorporeal circulation on the postoperative distribution of piperacillin in six patients undergoing aortic valve replacement. After a single dose administration of piperacillin/tazobactam 4/0.5g, interstitial fluid concentrations of free piperacillin in skeletal muscle and subcutaneous adipose tissue were significantly lower in patients than in healthy volunteers, with $AUC_{interstitium}/AUC_{serum}$ ratios averaging 0.27 and 1.22 in muscle and 0.25 and 0.43 in subcutis, respectively. The investigators concluded that these lower antimicrobial concentrations at target sites in patients were at least partially due to increased capillary permeability and subsequent accumulation of fluid in the interstitial space of soft tissues as a response to the trauma of surgery, and that this may have resulted in inadequate t>MIC for high-MIC strains, leading to therapeutic failure in some patients. Using the same technique, Joukhadar et al.[67] assessed piperacillin penetration in soft tissues of six septic patients compared with a group of correctly matched healthy volunteers. They observed that interstitial fluid concentrations of piperacillin in soft tissues of septic patients, due to capillary leakage, were 5- to 10-fold lower than in plasma and that $AUC_{interstitium}/AUC_{plasma}$ ratios were 3- to 4-fold lower than in the control group of healthy volunteers (with concentration ratios being 0.08–0.27 in patients and ≤0.94 in healthy volunteers), concluding that higher than currently administered dosages of piperacillin (4g three times daily) should be considered for patients with septic shock, preferably by shortening the dosage interval.

The penetration of cefpirome in the interstitial space fluid of skeletal muscle was measured by microdialysis in 12 patients with septic shock and in six age-matched healthy volunteers.[68] After cefpirome 2g single dose, both peak plasma concentration and muscle interstitial AUC from 0 to 6 hours (AUC_6) of cefpirome were found to be significantly lower in septic patients compared with healthy volunteers (C_{max} 62 ± 4 vs 127 ± 15 mg/L; AUC_6 9.80 ± 0.72 vs 15.52 ± 1.44 mg • min/mL) because of interstitial oedema resulting from capillary leakage in response to the infection, suggesting that in order to ensure effective concentrations at the infection site even in the presence of less susceptible bacteria

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such as *P. aeruginosa* (MIC that inhibits the growth of 90% bacteria [MIC_{90}] >16 mg/L) the dosage interval for cefpirome 2g should be shortened from 12 hours to 8 hours in patients with sepsis.

In 15 critically ill adult patients with a median Acute Physiology and Chronic Health Evaluation (APACHE) II score of 12 and a mean creatinine clearance of 61 mL/min receiving ceftazidime 2g every 8 hours, the V_d of ceftazidime at steady-state was more than 4-fold greater than in historical controls (56.91 ± 25.93 vs 13.9 ± 1.9L; $p < 0.001$) due to increased extracellular volume as a result of capillary leak.[69] Interestingly, despite no significant differences in ceftazidime clearance compared with control (9.06 ± 4.79 vs 6.64 ± 0.67 L/h), serum ceftazidime concentration dropped below the MIC_{90} for *P. aeruginosa* (8 mg/L) just after 6 hours in one patient and after 8 hours in another four patients, suggesting that in the presence of less susceptible pathogens, standard ceftazidime dosages (2g three times daily) may be insufficient for optimal drug exposure in some septic patients. Hanes et al.,[70] assessing disposition of ceftazidime 2g three times daily in critically ill trauma patients with Gram-negative nosocomial pneumonia, showed that both V_d (0.32 ± 0.14 vs 0.21 ± 0.03 L/kg; $p = 0.003$) and total body clearance (2.33 ± 1.06 vs 1.58 ± 0.23 mL/min/kg; $p = 0.003$) of ceftazidime were substantially increased in comparison with healthy volunteers. Since this dosage regimen was estimated enabling t>MIC only for 74% of the dosage interval for causative pathogens with an MIC of 8 mg/L, they concluded that caution should be taken in using the 2g three times daily dosage regimen of ceftazidime for the treatment of pneumonia caused by *P. aeruginosa* or *Acinetobacter* species in critically ill trauma patients, suggesting that continuous intravenous infusion by maintaining serum concentrations above the MIC for the entire day may circumvent this problem.

McKindley et al.[71] assessed the pharmacokinetics of aztreonam (2g every 8 hours) and imipenem (500mg every 6 hours) in two parallel groups of post-trauma critically ill patients affected by nosocomial pneumonia with an Injury Severity Score ≥10. After 2–3 days of treatment, as a consequence of trauma, the resulting V_d of both drugs was significantly increased in the patients compared with historical controls (aztreonam 0.42 ± 0.19 vs 0.21 ± 0.06L; $p < 0.05$; imipenem 0.35 ± 0.13 vs 0.23 ± 0.03L; $p < 0.05$), suggesting that standard initial dosages of aztreonam and imipenem may result in lower concentrations in these critically ill patients.

In summary, all of these studies suggest that higher dosages for most hydrophilic antimicrobials (either aminoglycosides or β-lactams) should be considered to ensure therapeutic concentrations in critically ill patients with oedema.

4.1.2 Fluid Therapy or Parenteral Nutrition

Aggressive intravenous fluid therapy may contribute to expanding extracellular water and causing dilution of hydrophilic antimicrobials in the extracellular compartment in critically ill patients.

In a case report concerning a 19-year-old critically ill post-trauma male patient receiving a standard dosage of amikacin 1g once daily for 35 consecutive days because of a Gram-negative respiratory infection, Botha et al.[72] clearly showed that, as a result of copious administered fluid supplements (range 2.94–5.62 L/day), the V_d of amikacin was substantially increased with significant daily fluctuations occurring throughout therapy (from 16.23L on day 4 to 39.66L on day 30). They concluded that amikacin peak plasma concentrations should be frequently monitored in critically ill patients receiving fluid supplements. Likewise, the V_d of vancomycin was found to be almost doubled on day 2 versus day 8 of therapy (0.81 L/kg vs 0.44 L/kg) in critically ill infants treated with a standard vancomycin dosage of 10 mg/kg every 6 hours, probably because of initial aggressive fluid resuscitation.[73] This led the investigators to conclude that monitoring vancomycin serum levels may be beneficial in this population. In addition, fluid load was also considered to be a possible co-factor in increasing the V_d of cefpirome in septic patients.[68,116]

Total parenteral nutrition may also contribute to expanding the V_d of hydrophilic antimicrobials in critically ill patients.

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Ronchera-Oms et al.[74] assessed the influence of total parenteral nutrition on the pharmacokinetics of gentamicin in critically ill adult patients with severe Gram-negative infections. They showed a significantly higher V_d of gentamicin in patients receiving total parenteral nutrition compared with those receiving only fluid therapy (0.43 ± 0.12 vs 0.34 ± 0.08 L/kg), and suggested that higher dosages of gentamicin should be administered to attain therapeutic peak concentrations of gentamicin in parenterally fed critically ill patients.

In summary, substantial fluid load and parenteral nutrition should be considered major causes of antimicrobial dilution, possibly leading to undertreatment.

4.1.3 Pleural Effusion

Although pleural effusion may be related to infection, it should not be overlooked that sometimes fluid extravasation in the pleural cavity may also occur because of hypoalbuminaemia[117] or other conditions. Despite only a few studies in the literature specifically addressing the issue of increased V_d of antimicrobials in patients with pleural effusions (for example Etzel et al.[75] for gentamicin and tobramycin), undoubtedly the penetration in pleural exudate shown by several hydrophilic antimicrobials[118-131] and the resulting dilution may justify the need for higher dosages in the presence of significant pleural effusion. Consistent with the variable pharmacokinetics of the different drugs in animal models,[132] the required dosage adjustments could be unpredictable, and therefore should be based whenever possible on the measurements of serum levels of drugs in these circumstances.

4.1.4 Ascites and Peritoneal Exudate

In patients with advanced liver diseases, plasma and blood volume expansion,[133] ascites related to portal hypertension and decrease in albumin synthesis, by causing an increase in the extracellular compartment fluid,[61] may lead to significant increases in V_d of hydrophilic antimicrobials.

This was documented in early studies concerning both aminoglycosides (gentamicin,[134] amikacin,[135] tobramycin[136]) and β-lactams (ampicillin,[137] ceftazidime,[138,139] ceftriaxone,[140,141] cefotaxime,[141] piperacillin,[142] aztreonam[143]), and has been confirmed more recently in a population pharmacokinetic study assessing the effects of ascites and hepatic function on vancomycin disposition in patients with cancer.[76] Interestingly, whereas no major changes in clearance related to liver function was observed, the V_d of vancomycin was found to be significantly increased in patients presenting with hepatic failure and ascites (1.02 ± 0.25 L/kg) compared with those presenting with hepatic failure but without ascites (0.75 ± 0.17 L/kg) or those without hepatic failure (0.64 ± 0.15 L/kg).[76] On this basis, the investigators suggested that dosage adjustments during vancomycin treatment may be needed in patients with hepatic failure only in the presence of ascites.

Also, the formation of exudative fluid in the peritoneal cavity as a result of intra-abdominal infections may, in turn, be responsible for a larger V_d for hydrophilic antimicrobials. Interestingly, this site of pathological increase of V_d may behave like a deep compartment with long elimination half-life, and hence the pharmacokinetics may be very different in this compartment than in others. In a pharmacokinetic study assessing ceftazidime disposition in patients with severe intra-abdominal infections treated with ceftazidime 4.5 g/day administered either as continuous (n = 12) or intermittent (n = 6) intravenous infusion, the V_d of ceftazidime was found to be significantly higher than in healthy volunteers (0.28 vs 0.18 L/kg), probably owing to the presence of peritoneal exudate (volume of exudate 200–3200mL).[77] Continuous intravenous infusion resulted in more favourable concentrations in both plasma and peritoneal exudate, but since the exudate to plasma AUC ratio was about 0.6, the investigators concluded that higher dosages of ceftazidime may be necessary when treating patients with severe intra-abdominal infections caused by less susceptible pathogens such as *P. aeruginosa*.

Whatever the mechanism responsible for fluid extravasation, as a consequence of drug dilution in the extra volume, in patients with severe liver diseases and ascites, as well as in patients with peritoneal exudate, often the dosages of hydrophilic or

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moderately lipophilic antimicrobials should not be reduced (unless simultaneously impaired renal function may decrease plasma clearance), and therapeutic drug monitoring (TDM) may be helpful with the intent of optimising drug exposure in this subpopulation.[61,144] Of note, Lugo and Castaneda-Hernandez[145] showed that in patients with sepsis and cirrhosis the V_d of amikacin was significantly increased (0.67 L/kg) not only in comparison with healthy volunteers (0.25 L/kg) but also with respect to the general septic population without cirrhosis (0.47 L/kg). Subsequently, the population pharmacokinetic parameters estimated in this study were successfully used as *a priori* distribution in a Bayesian forecasting method with the intent of improving prediction of plasma concentrations with acceptable precision.[145]

4.1.5 Mediastinitis

A special issue possibly affecting antimicrobial disposition in post cardiac surgery patients is represented by mediastinitis. Although haematoma or fluid collection occurring in the mediastinum after sternotomy for cardiac operation is usually of moderate extent,[146] in the presence of mediastinitis third space problems due to the sequestration of protein-rich fluids that may require albumin administration[147] may occur.[148] It should not be overlooked that significant dilution of hydrophilic antimicrobials as a consequence of third space sequestration in the mediastinum may require higher dosages in order to achieve therapeutic concentrations.

4.1.6 Indwelling Post-surgical Drainages

A frequently underestimated cause of antimicrobial loss ('false increase in V_d') in surgical patients may be the presence of indwelling drainages positioned after major thoracic and abdominal operations. Buijk et al.[77] found that after a loading bolus dose of ceftazidime 1g and a daily maintenance dosage of 4.5g as continuous intravenous infusion, on day 4 the mean ceftazidime concentration in peritoneal exudate in patients with intra-abdominal infections was 26.6 mg/L, with a total 24-hour volume of drained exudate of 1600mL. Although average drainages-related loss of ceftazidime was about 50mg daily, since daily volume of exudate was found to be as high as 4900mL in one instance, this loss might be even larger in some patients. Likewise, substantial concentrations of cefamandole were found in the haematoma fluid draining from the operation sites after hip replacement, averaging 7.2 mg/L 6–8 hours after administration of the first pre-anaesthesia dose of 1g, and 15.0 mg/L and 10.4 mg/L, 10–12 hours and 14–16 hours, respectively, with a further dose given after 8 hours.[149]

Therefore, considering that drainages may represent a pathway of antimicrobial loss and may thereby contribute to lower antimicrobial levels, larger dosages of hydrophilic antimicrobials may sometimes be necessary for optimal treatment of this subpopulation, especially when other co-factors responsible for dilution may be simultaneously present. TDM may therefore be of great value in such patients for clinicians with the intent of tailoring drug exposure in the individual patient.

4.1.7 Hypoalbuminaemia

Hypoalbuminaemia is a frequently occurring condition in critically ill patients as a consequence of increased albumin capillary escape rate through leaky endothelium, or fluid overload or malnutrition. By reducing plasma oncotic pressure, hypoalbuminaemia may contribute to fluid extravasation and antimicrobial dilution, whereas the increase in the free fraction of drugs may increase their V_d.

In a recent population pharmacokinetic study on amikacin disposition in patients with haematological malignancies, despite the negligible plasma protein binding of this aminoglycoside, hypoalbuminaemia was proven to be one of the most important covariates in explaining interindividual pharmacokinetic variability of amikacin in this population.[78] Particularly, due to the significant contribution in increasing amikacin V_d, the investigators recommended that the initial dosage of amikacin in patients with haematological malignancies with hypoalbuminaemia and normal renal function should be about 1.6-fold higher than in the standard patient.[78]

When considering renally excreted highly albumin-bound antimicrobials (i.e. teicoplanin and ceftriaxone) it should not be overlooked that by in-

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creasing the unbound fraction, hypoalbuminaemia may promote not only more extensive distribution, but also higher renal clearance.[98,150]

In a renal transplant patient treated with teicoplanin at a daily dose of 8.57–11.42 mg/kg because of sepsis resulting from coagulase-negative staphylococci, Pea et al.[79] recently showed that severe hypoalbuminaemia (1.73–2.58 g/L) may significantly enhance both distribution and elimination of teicoplanin during renal replacement therapy with continuous veno-venous haemofiltration (CVVH). Of note, the increased free moiety of teicoplanin resulted in an almost doubled sieving coefficient (0.17 vs <0.10), suggesting that teicoplanin clearance may be enhanced in patients with sepsis undergoing CVVH and presenting with major hypoalbuminaemia. TDM is thus strongly advisable considering that unexpectedly high doses could be needed to ensure optimal therapeutic concentrations.[79]

Likewise, hypoalbuminaemia, together with multiple drug infusions and volume expansion treatments, was considered one of the most important cofactors in contributing to low steady-state trough levels (<10 mg/L in 89% of patients) observed during teicoplanin treatment at a dosage of 10 mg/kg/day in 21 critically ill children aged between 7 days and 12 years. The investigators concluded that higher dosages should be administered to ensure optimal treatment in these conditions.[80]

In ten critically ill patients with severe sepsis treated with intravenous ceftriaxone 2g once daily, the severe hypoalbuminaemia (22 ± 6.1 g/L) resulted in a substantial increase in V_d and an almost doubling of drug clearance (41.3 ± 11.7 vs 19.8 ± 2.5 mL/min) in patients with normal renal function compared with healthy volunteers, thereby lowering trough concentrations below the desired threshold (<8 mg/L) with possible suboptimal exposure in five of ten patients.[81] Based on these findings, the investigators suggested either shortening the dosage interval or administering the same dose as continuous intravenous infusion to ensure optimal ceftriaxone concentrations over the entire dosage interval in critically ill patients with severe hypoalbuminaemia and normal renal function.[81]

Interestingly, iatrogenic hypoalbuminaemia induced by hydroxyethyl starch in postsurgical adult patients was found, on the contrary, to alter mainly the V_d of ceftriaxone.[82] As expected, the significantly higher free fraction of ceftriaxone observed in patients versus correctly matched normoalbuminaemic healthy volunteers (14% and 46% in patients vs 10% and 18% in volunteers at 0 hours and 24 hours after dosage, respectively) caused an increase in V_d, but not a greater total clearance, probably due to saturation of the biliary excretion of the free fraction of ceftriaxone. On the basis of these findings, the investigators concluded that the increased free concentrations of ceftriaxone might have even enhanced effectiveness on this particular occasion.[82]

In summary, higher dosages of hydrophilic antimicrobials may frequently be necessary to adequately treat critically ill patients presenting with severe hypoalbuminaemia, and TDM may be helpful to streamline therapy for these patients.

4.2 Causes of Enhanced Renal Clearance

Enhanced renal clearance of hydrophilic and moderately lipophilic antimicrobials may be expected whenever pathophysiological or iatrogenic conditions increasing renal blood flow – and thereby glomerular filtration and tubular secretion rates – may occur.

4.2.1 Burns

Several factors may substantially alter the pharmacokinetics of antimicrobials in patients with extensive third degree burns (>30–40% body surface area).

According to the elapsed time from the event (less than or more than 48 hours), different pathophysiological changes may occur in burn patients.[151,152]

In the first 2 days, namely the acute or resuscitation phase of thermal injury, hypovolaemia possibly leading to a drop in renal blood flow and glomerular filtration rate may occur as a result of protein-rich fluid loss due to altered capillary permeability. However, during this phase the resultant partial impairment of renal clearance may be counteracted by

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nonrenal/hepatic clearance via the weeping of the antimicrobial out of the body in abundant exudates from the burns, so that the net pharmacokinetic effect could be that there is no need for major dosage adjustments of antimicrobials to ensure therapeutic concentrations in the first 48 hours.

Indeed, from a pharmacokinetic point of view perhaps more relevant pathophysiological changes may occur beyond 48 hours when, after providing appropriate fluid replacement, the hypermetabolic phase usually begins. This period is frequently characterised by an increase in cardiac output leading to enhanced renal blood flow and in turn glomerular filtration rate, which may become significantly increased compared with healthy controls, as suggested by creatinine clearance values being sometimes as high as 240 mL/min.[152,153] This phase usually lasts several days, with the intensity progressively decreasing according to the elapsed time from thermal injury. As a consequence, the renal clearance of most hydrophilic and moderately lipophilic antimicrobials is expected to increase significantly during the hypermetabolic phase,[151] as observed in several pharmacokinetic studies concerning aminoglycosides (gentamicin,[154,155] amikacin,[156] tobramycin[157]), β-lactams (ticarcillin/clavulanic acid,[158] cefepime,[83] ceftazidime,[159] meropenem,[160] aztreonam[161]), glycopeptides (vancomycin,[162-164] teicoplanin[165,166]) and even partially renally eliminated fluoroquinolones (ciprofloxacin[167]), although other studies of imipenem,[168] piperacillin[169] and ciprofloxacin[170] failed to show this.

The pharmacokinetics of cefepime in burn patients was assessed in two recently published studies. Bonapace et al.[83] showed that in 12 burn patients presenting with extremely high creatinine clearance values (104–191 mL/min) receiving a single 2g dose of cefepime, drug V_d was almost doubled (0.43 L/kg vs 0.18–0.24 L/kg) and renal clearance increased by 10–30% compared with healthy volunteers. According to the plasma concentration-time profiles simulated by means of patients' pharmacokinetic estimates, the investigators showed that, in all of the patients, to ensure a t>MIC for at least 50% of the dosage interval, both 2g twice daily and 1g three times daily of cefepime should be enough, but to ensure a t>MIC for the entire dosage interval, higher dosages (2g three times daily) should be considered appropriate. Sampol et al.[84] assessed the disposition of cefepime 2g after the first and fifth dose in a small population of burn patients (n = 6), with mean burn surface area of 31.5%. Different to the previous study,[83] only an increase in V_d (0.36 L/kg vs 0.18–0.24 L/kg) without any major changes in clearance and $t_{1/2}\beta$ of cefepime compared with healthy volunteers was found,[84] leading the investigators to conclude that no changes in the standard dosage of cefepime (2g every 12 hours) are needed in burn patients. However, in a commentary on this latter study, Weinbren[171] appropriately highlighted that pharmacokinetic studies of antimicrobials in burn patients should also be conducted in the late post-injury period and in a large number of patients and heterogeneous populations, in order to define appropriate dosages applicable throughout the entire post-injury period.

In any case, given the complex pathophysiological changes, the frequent need for more aggressive dosages and the wide interindividual pharmacokinetic variabilities, several investigators have advocated a major role for TDM in optimising antimicrobial therapy in severely burnt patients, not only for drugs with a narrow therapeutic index (i.e. aminoglycosides[155,172] or glycopeptides[153,164-166,173]) but, whenever possible, also for other hydrophilic antimicrobials, such as β-lactams.[151,152,174]

For a comprehensive review of antimicrobial disposition in burn patients, readers are referred to the works of Jaehde and Sorgel[151] and Weinbren.[152]

4.2.2 Hyperdynamics

The hyperdynamic conditions frequently occurring in the early phase of sepsis may be responsible for an increase in cardiac output and renal blood flow that may, in turn, lead to enhanced glomerular filtration rate and tubular secretion of renally eliminated drugs in critically ill patients.[60,175]

Changes occurring in gentamicin pharmacokinetics related to the intensity of cardiac output were assessed by Tang et al.[65] during treatment for

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Gram-negative-related sepsis. Although, when considering the septic population as a whole, the clearance of gentamicin was decreased compared with controls, after splitting patients into two groups according to cardiac index the clearance of gentamicin was found to be 1.5-fold higher in hyperdynamic septic patients (4.1 ± 0.59 L/min/m^2) than in hypodynamic septic patients (2.7 ± 0.43 L/min/m^2) or controls (2.4 ± 0.2 L/min/m^2).

Similarly, in critically ill trauma patients treated with ceftazidime 2g every 8 hours or 60 mg/kg continuous intravenous infusion, drug clearance was found to be significantly higher than in healthy volunteers (2.35 ± 0.89 vs 1.58 ± 0.23 mL/min/kg), so that in the presence of infections due to less susceptible pathogens, the application of continuous intravenous infusion was advocated to circumvent the problem.[70]

Pea et al.[85] evaluated levofloxacin disposition in critically ill patients treated with a high dosage regimen of 500mg every 12 hours because of early-onset ventilator-associated pneumonia. Levofloxacin renal clearance was significantly higher than in healthy volunteers (3.40 vs 2.42 mL/min/kg), probably due to the enhancement of both glomerular filtration rate and tubular secretion as a result of hyperdynamic conditions. The investigators concluded that this improved dosage should be considered appropriate for the treatment of critically ill patients showing high estimated creatinine clearance.

Likewise, Lipman et al.[176] assessed the pharmacokinetics of ciprofloxacin at very high doses (400mg three times daily) in 18 critically ill patients who had severe sepsis and no major impairment of renal function (creatinine clearance ≥30 mL/min). Interestingly, although in this population mean ciprofloxacin clearance was similar to that observed in healthy volunteers (0.4 mL/min/kg), the coefficient of variation was as high as 50% in critically ill patients versus only 11% in historical controls, suggesting that very high interindividual pharmacokinetic variability may occur in this setting. Additionally, although not directly addressed by the investigators, it may be hypothesised that the very high ciprofloxacin clearance found in at least one patient (0.82 mL/min/kg) might have been related to the hyperdynamic condition during sepsis. Nevertheless, ciprofloxacin 400mg three times daily was considered suitable for ensuring optimal exposure (in terms of either C_{max}/MIC or AUC/MIC) in critically ill patients with severe sepsis.

In ten critically ill patients with sepsis, trough plasma concentrations of cefepime after multiple administrations of 2g every 12 hours were particularly low (<1 mg/L in four patients and <4 mg/L in five patients) owing to increased drug renal clearance.[86] On this basis, the investigators suggested the daily dosage of cefepime should be increased to 6g in critically ill patients with normal renal function, and in order to maintain therapeutic concentrations during the whole dosage interval a more refracted dosage regimen (i.e. 1g every 4 hours or continuous intravenous infusion) would be preferable. Recently, the importance of increased glomerular filtration rate in enhancing clearance and lowering trough levels of either cefepime and cefpirome after administration of standard dosages in critically ill patients has been further emphasised by the same investigators.[87] They suggested overcoming this problem by shortening the dosage interval or applying continuous intravenous infusion, and to measure creatinine clearance more frequently in ICU patients to allow prediction of low cephalosporin levels at the bedside.

In summary, all these studies underline the necessity of defining higher than presently recommended dosages for most renally excreted antimicrobials in the treatment of septic patients presenting with normal renal function.

4.2.3 Haemodynamically Active Drugs

Although the role of haemodynamically active drugs (HADs), i.e. dopamine, dobutamine and furosemide (frusemide), aimed at improving haemodynamics and renal blood flow,[177-179] is generally recognised in the ICU setting,[180,181] their importance in affecting the disposition of antimicrobials in critically ill patients has often been neglected in the past.[98]

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Pea et al.[88] first assessed the potential role of dopamine, dobutamine and furosemide in altering the disposition of vancomycin in cardiac surgical patients. Serum trough levels of vancomycin were significantly decreased in 8 of 18 patients during co-treatment with at least two of these HADs (dobutamine + furosemide in four patients and dopamine + dobutamine + furosemide in another four patients), so that dosages 1.25- to 1.90-fold higher than recommended by Moellering's nomogram[182] had to be administered to maintain therapeutic concentrations. Interestingly, withdrawal of coadministered HAD in four of these eight patients occurred during vancomycin treatment and was followed by a subsequent marked increase of vancomycin trough levels. This suggested that during co-treatment, renal clearance of vancomycin was significantly increased as a result of enhanced glomerular filtration rate and tubular secretion due to the synergistic effect of HAD on cardiac output and/or renal blood flow.[88] The investigators concluded that TDM for the pharmacokinetic optimisation of vancomycin is strongly recommended in these situations.

Likewise, dopamine and furosemide were considered by the same investigators to contribute to the enhancement of renal clearance of levofloxacin observed in some ICU neurosurgical patients during treatment with levofloxacin 500mg twice daily for ventilator-associated pneumonia.[85] In the same study, co-treatment with mannitol administered to lower intracranial pressure was, in turn, considered to increasing levofloxacin clearance in some other patients, taking into account that this osmotic diuretic may improve renal blood flow.[183]

In critically ill patients with severe sepsis, the clearance of ceftriaxone at a dosage of 2g every 24 hours was found to be almost doubled in comparison with healthy volunteers.[81] Among the possible factors responsible for this, the use of inotropes was considered to significantly contribute in three of ten patients, therefore the investigators recommended a more aggressive dosage regimen of ceftriaxone in this setting by decreasing dosage interval or applying continuous intravenous infusion.

In summary, given the frequent simultaneous use of antimicrobials and HAD in ICU patients, clinicians must be aware of possible drug-drug interactions altering the pharmacokinetics of antimicrobials. TDM is strongly recommended for optimisation of exposure in these circumstances.

4.2.4 Acute Leukaemia

Most hydrophilic antimicrobials have been shown to exhibit altered pharmacokinetics in patients with haematological malignancies,[78,89,184-188] and several investigators documented that enhancement of renal function may partially account for this. For example, higher than normally expected dosages of vancomycin (38 mg/kg/day) as a result of enhanced renal clearance were shown to be necessary to ensure therapeutic concentrations in patients with haematological malignancies.[89] Similar findings were also observed with other drugs (namely amikacin[78,186] and teicoplanin[187]) and further confirmed with vancomycin.[90,91]

Recently, Pea et al.[92] assessed plasma teicoplanin trough levels achievable in patients with acute leukaemia empirically treated with teicoplanin at standard (n = 11) or high (n = 22) dosage regimens. It was observed that standard teicoplanin dosages (an average loading dose of 6.2 mg/kg every 12 hours for three doses followed by 6.2 mg/kg every 24 hours) in patients with acute leukaemia might achieve only much lower concentrations than achievable in healthy volunteers (none of 11 patients achieved the recommended trough level of 10 mg/L in the first 72 hours), whereas a more aggressive dosage regimen (an average loading dose of 12.2 mg/kg + 6.1 mg/kg 12 hours apart on day 1 and 9.2 mg/kg + 6.1 mg/kg 12 hours apart on day 2, followed by a daily maintenance dose of 6.1 mg/kg every 12 hours) may enable, in most patients with normal renal function, trough concentrations of teicoplanin exceeding 10 mg/L at 24 hours (13 of 22 patients) and approaching 20 mg/L at 72 hours (10 of 22 patients). Some investigators believe that enhancement in renal clearance of hydrophilic antimicrobials in febrile neutropenic patients may be the consequence of fever and/or acute infectious disease.[189] However, our contention is that, consistent

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with an acute protein load increasing renal blood flow,[190] an increased glomerular filtration rate occurring as a consequence of huge renal load of proteic cellular catabolites deriving from massive lysis of circulating cells may be a co-factor, at least in the early post-chemotherapy period.[92]

Besides enhancement of renal function, it should not be overlooked that patients with acute leukaemia may frequently present other underlying situations that may also increase the V_d of drugs (i.e. hypoalbuminaemia, fluid overload and parenteral nutrition). Therefore, higher than currently suggested dosages may probably be necessary for most hydrophilic antimicrobials, and TDM with the intent of ensuring optimal exposure in this special population should be performed wherever available. It is worthy to note that we have recently shown that the use of continuous intravenous infusion may be a helpful tool for maximising pharmacodynamic exposure with ceftazidime in this special population.[191]

4.2.5 Drug Abuse

There are only very few studies in the literature assessing the possible role of drug abuse in altering the disposition of antimicrobials. In 1985, King et al.[93] evaluated the pharmacokinetics of gentamicin and tobramycin in 18 drug abusers, observing that in most patients (66%) a faster elimination of these aminoglycosides occurred. Similar findings in intravenous drug abusers were also observed with two glycopeptides (teicoplanin and vancomycin) in subsequent studies conducted by Rybak et al.[94,95] Interestingly, in all three studies the investigators agreed that the frequently increased glomerular filtration rate observed in drug abusers was the pathophysiological mechanism responsible for the enhanced clearance of these antimicrobials, and concluded that frequently more aggressive dosages may be necessary to ensure therapeutic concentrations in this subpopulation.

To the best of our knowledge no other major study evaluating the pharmacokinetics of antimicrobials in this kind of patient population has been published recently; however, it seems extremely reasonable that similar enhanced elimination may occur for most renally eliminated hydrophilic and moderately lipophilic antimicrobials. Appropriate studies are advisable to confirm this hypothesis, but physicians should meanwhile be aware that higher dosage regimens of most β-lactams should be appropriate whenever very high values of creatinine clearance are estimated in intravenous drug abusers, and that even in this circumstance TDM may be helpful in tailoring antimicrobial therapy to individual patients.

4.3 Causes of Reduced Renal Clearance

4.3.1 Renal Failure

In critically ill patients, renal failure may occur because of several different underlying diseases (i.e. trauma, multiple organ failure, extensive burns, cardiogenic or hypovolaemic shock) or it may be iatrogenically induced by nephrotoxic therapies (i.e. aminoglycosides, vancomycin, ciclosporin, methotrexate). Moreover, it should not be overlooked that the simultaneous use of cathecholamines, by decreasing renal blood flow, may be associated with a reduced clearance of renally eliminated drugs. Lugo and Castaneda-Hernandez[96] showed that the use of cathecholamines or even very high-dose dopamine (15 mg/kg/min) was significantly associated with a decrease of amikacin renal clearance in 30 critically ill patients with severe Gram-negative sepsis.

In these situations a reduction in the average daily dosage of most hydrophilic and moderately lipophilic antimicrobials may be required to avoid overexposure. In reality, the choice of appropriate dosage may be particularly difficult when application of renal replacement therapies (RRTs) is required in ICU patients.

An in-depth analysis of the role of RRTs in modifying antimicrobial disposition is beyond the aims of this review and readers are referred to other more comprehensive reviews,[192,193] however, it must be mentioned that extraction ratios of different antimicrobials may vary greatly according to both the intrinsic properties of the antimicrobials (physicochemical characteristics, molecular weight, plasma protein binding, elimination route) and the characteristics of the applied RRT. Generally, intermittent dialysis (usually 4 hours every 2 days) removes,

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by means of diffusion, only renally eliminated antimicrobials that have sufficiently low molecular weight (<700) and negligible protein binding (most β-lactams, aminoglycosides, some fluoroquinolones). On the other hand, CVVH or continuous venovenous haemodiafiltration by means of convection or convection plus diffusion, respectively, may also remove bulky antimicrobials (i.e. vancomycin); and through continuous application 24 hours a day they are often very efficacious techniques in drug removal, especially when very high replacement flows are selected.[194]

As a consequence, TDM may be especially important in tailoring antimicrobial therapy in patients undergoing RRT.

4.3.2 Muscle Wastage and Long-Term Bedridden Patients

Although kidney function is frequently assessed on the basis of serum creatinine and estimated creatinine clearance, in the presence of prolonged immobilisation and/or extensive muscle trauma these parameters may often fail to estimate renal function appropriately in critically ill patients.[115] In a patient with spinal cord injury affected by staphylococcal sepsis and *Clostridium difficile* colitis, the inappropriate estimation of creatinine clearance on the basis of serum creatinine and the Cockcroft and Gault formula[195] was responsible for vancomycin overdosage.[97] Subsequent measurement of 24-hour creatinine clearance revealed the actual value was 61% lower than predicted as a result of reduced creatinine production due to muscle atrophy.[196]

Likewise, dosage adjustments of antimicrobials based on estimated renal function may cause antimicrobial overdosage whenever ICU patients are bedridden for a long time (i.e. >3–4 weeks).[197]

Therefore, in these situations direct measurement of creatinine clearance is strongly advisable in order to avoid overestimation of renal clearance of antimicrobials, and thereby overtreatment.

5. The Importance of a Multidisciplinary Team in Tailoring Antimicrobial Therapy in Critically Ill Patients

Considering all the aforementioned factors should be helpful for clinicians in appropriately handling antimicrobials in critically ill patients. However, specifically regarding antimicrobial use, a decisional approach involving both the infectious disease specialist and the clinical pharmacologist may surely be beneficial to streamline antimicrobial therapy in an attempt to maximise the outcome in these difficult-to-treat patients.

The valuable role of the infectious disease specialist in appropriate management of antimicrobial use has been efficaciously debated by Petrak et al.[198] who emphasised, among others, the importance of instituting programmes of antimicrobial stewardship.

In addition, considering that in critically ill patients several of the previously outlined underlying pathophysiological or iatrogenic situations may often coexist in the same individual and that the pharmacokinetic variability may be partially unpredictable, the antimicrobial policy may further benefit from the application of TDM.

Several studies support the major role of TDM in tailoring antimicrobial therapy in critically ill patients,[197,199] and many clinical trials have demonstrated a positive impact of TDM on clinical outcome[114,200,201] and cost of hospitalisation,[202] and also emphasised the importance of the consultant clinical pharmacologist. Hansen et al.[114] evaluated the influence of the clinical pharmacologist in optimising gentamicin dosage in critically ill patients by comparing conventional TDM versus so-called intensified TDM, which differed by including an associated clinical pharmacologist who was responsible for the dosage recommendations. Intensified TDM was significantly more efficacious in ensuring optimal peak plasma exposure to gentamicin, reducing time of hospitalisation, and preventing drug-related nephrotoxicity.[114] Likewise, at the Medical School, University of Udine, Italy, we have recently assessed the role of TDM in optimising vancomycin exposure in critically ill patients by comparing dos-

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Institute of Clinical Pharmacology & Toxicology - University of Udine - Italy

Patient's data collection form for TDM of antimicrobial agents

Hospital department

Physician sending enquiry

Patient's data

Male ☐ Female ☐

Birth date ..... Weight (kg) ..... Height (cm) .....

sGOT ..... sGPT ..... Albuminaemia ..... sCr ..... CL_{CR} .....

Underlying pathophysiological conditions infection site .....

fluid extravasation (pleuritis – mediastinitis – ascites – pericarditis – others.....) drainages

dialysis CVVH CVVHDF obesity (BMI.....)

burns (%)..... from days.....

hydration status sepsis haematological malignancies VAP

Aetiological agent ..... **MIC (mg/L)** .....

Drug therapy

Antibacterial agent

Haemodynamically active drugs/diuretics:

furosemide dopamine dobutamine
mannitol

Reasons for TDM enquiry

PK interactions
possible undertreatment

possible overtreatment
impairment of renal function

others

Data for TDM

Date	Sampling time	Drug	Dosage	Time of adms	Time of previous adms		

Comments:

Fig. 3. Patient data collection form for therapeutic drug monitoring (TDM) of antimicrobials. **adms** = administration; **BMI** = body mass index; **CL_{CR}** = creatinine clearance; **CVVH** = continuous veno-venous haemofiltration; **CVVHDF** = continuous venovenous haemodiafiltration; **MIC** = minimum inhibitory concentration; **PK** = pharmacokinetics; **sCr** = serum creatinine; **sGOT** = serum glutamic-oxaloacetic transaminase; **sGPT** = serum glutamic-pyruvic transaminase; **VAP** = ventilator-associated pneumonia.

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age adjustment suggested by the clinical pharmacologist on the basis of TDM and Bayesian forecasting with that based on Moellering's nomogram.[197] Dosage adjustment based on the Bayesian method enabled more frequent achievement of the desired target steady-state trough level of vancomycin (10 mg/L); several underlying pathophysiological conditions at least partially responsible for the unreliability of Moellering's nomogram in this population were also highlighted.[197]

Accordingly, at our institute several of the antimicrobials most frequently used in the critical care setting, namely meropenem, ceftazidime, levofloxacin and ciprofloxacin, and not only narrow therapeutic index antimicrobials such as aminoglycosides and glycopeptides, are routinely monitored in real time with the intent of improving judicious use of antimicrobials. To facilitate clinicians' work and improve our consultation competence, a comprehensive data sheet (figure 3) with marked boxes including the most important variables that may affect drug disposition in critically ill patients has been developed.

6. Conclusion

The data reviewed herein support the opportunity of accurately assessing the particular underlying circumstances of each critically ill patient to optimise their antimicrobial therapy, considering the pharmacokinetics of each drug, so that the usefulness of a multidisciplinary team involving several pivotal skills – the clinical microbiologist, the infectious disease specialist and the clinical pharmacologist – may be advocated with the intent of supporting the intensivists and other specialists in the management of hospital antimicrobial policy.

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Correspondence and offprints: Dr *Federico Pea*, Institute of Clinical Pharmacology and Toxicology, University of Udine, P.le S. Maria della Misericordia 3, DPMSC, 33100 Udine, Italy.
E-mail: federico.pea@med.uniud.it

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