Antibiotic adjustment in CRRT

CRITICAL CARE NEPHROLOGY, 3/E

CHAPTER 176

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Key points

The management of infection in Intensive Care Unit represents an imperative challenge for critical care clinicians. At present, antibiotic dosing regimens are derived from studies on healthy volunteers and do not account for these major differences in drug make up.

- Critical illness is characterised by marked homeostatic disturbance, altered end-organ function, variable pre-existing comorbidity, and anthropometric irregularity. Such changes significantly distort the normal drugs PK profile, resulting in drug exposure that is markedly different from the “healthy volunteer”
- Renal Clearance is often modified in critical illness due to either acute kidney Injury or, on the other hand, to augmented renal clearance.
- CRRT have a profound effect on pharmacodynamics parameters of the antimicrobial agents
- Based on understanding of the principles drug removal by continuous renal replacement therapy, individual antimicrobial dosage and dosing interval may be estimated by mathematical equation

Abstract

The management of infection in Intensive Care Unit represents an imperative challenge for critical care clinicians. At present, antibiotic dosing regimens are derived from studies on healthy volunteers and do not account for these major differences in drug prescriptions. We summarized the pharmacokinetic/pharmacodynamics relationship changes in antimicrobial agents due to the typical homeostatic disturbance or altered end-organ function of the critical illness. We focused on how the renal clearance alterations or the Continuous Renal Replacement Therapy may affect individual antimicrobial dosage and dosing interval of the antimicrobial agents.

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1. BASIC PHARMACOLOGICAL PARAMETERS OF ANTIMICROBIAL AGENTS

The therapeutic effects of antibiotics depends on the achievement and maintenance of an adequate therapeutic free concentration at the site of infection. The concentration at the site of action is the result of several complex processes occurring in the body after drug administration Pharmacokinetics (PK) studies the evolution of the concentration of the admistered drug in the different compartments of the patient body over the time. After the administration, the plasma levels a given drug undergoes modification over time due to several of processes: absorption, distribution, metabolism and excretion (ADME)[1]. These changes represent the time-profile concentration, which is characterized by PK parameters, such a total body clearance (CL), Volume of distribution (V_d), plasma protein binding (PPB) and bioavailability (BA)[1]. Finally, in the site of the action at the required concentration, a drug produces the expected effect thanks of its mechanism of action. The Pharmacodynamics (PD) studies the biochemical and physiological effects of drugs and their mechanisms of action. Pharmacodynamics parameters relate the pharmacokinetic factors to the ability of an antimicrobial to kill or inhibit the growth of the pathogen organism antibiotics, and different antibiotic classes have different kill characteristics on bacteria. For this reason, the knowledge of the pharmacokinetic and pharmacodynamic properties of the antibiotics is essential for selecting the optimal dosage regimen. In the treatment of critically ill patients, the determination of individualized dosing regimens becomes even more difficult as a consequence of pathophysiological changes, organ failure and the need for organ-supportive therapy.

The pharmacokinetic changes induced by organ failure and critical illness must be considered and are particularly important for drugs with a small volume of distribution or high protein binding or both.

1.1. Pharmacokinetic parameters

Usually, in critically ill patients antimicrobial agents are administered by the intravenous (IV) route. Enteral administration (PO) route is not the first choice considering the altered adsorption processes due to oedema or inflammatory status of gastrointestinal mucosae.

The main pharmacokinetic parameters are the following:

- Bioavailability (BA), relating to antibiotics administered by an extravascular route (i.e. oral route)
- Plasma protein binding (PPB)
- Maximum (peak) plasma drug concentration achieved by a single dose (C_{max})
- Minimum plasma drug concentration during a dosing period (C_{min})

- Area under the plasma concentration-time curve (AUC)
- Volume of distribution (V_d)
- Clearance (CL)
- Half-life ($T_{1/2}$)

Bioavailability

Bioavailability refers to the degree that a drug is absorbed into the systemic circulation after extravascular administration: when the drug is administered by the IV route, 100% of the dose is bioavailable, whereas a drug administered by the PO route has to cross further barriers (absorption by gastric or intestinal mucosa, metabolism in liver also know first passage effect) to reach the systemic circulation, which can significantly reduce the final extent of a drug in the bloodstream.

In renal failure, numerous pathological factors and the clinical use of antacids, or alkalinizing agents may decrease gastrointestinal absorption. First-pass hepatic metabolism may also be diminished in uraemia, leading to increased serum levels of oral antibacterial agents[2].

Plasma protein binding

Plasma protein binding influences the V_d, the CL and the drug clearance during Renal Replacement Therapy (RRT) of many antibiotics. Exclusively, the plasma free (unbound) moiety of drugs is able to diffuse in the body and to be cleared off from plasma by kidney, liver or extracorporeal clearance.

Plasma drug concentration (C_{max}, C_{min}, AUC)

After PO, at the time when the rate of the drug entering the plasma (absorption) and the rate of the drug disappearing from the plasma (distribution and elimination) are equal, or at completion of IV infusion, the maximal concentration (C_{max}) is reached. Thereafter, the rate of distribution or elimination of the drug exceeds the rate of drug absorption, and the plasma concentration starts to decline to a minimal concentration (C_{min}). The Area Under the plasma concentration-time Curve (AUC) is a pharmacokinetic measure that indicates the exposure to a drug during the full dosing interval (***Figure 1***).

When starting an antibiotic drug therapy, the loading dose (LD) is administered in order to rapidly achieving therapeutically effective concentrations, whereas the maintenance doses (MD) are administered in order to maintain the effective levels over time by replacing the amount eliminated from the body during the dosing interval. Plasma levels for a given drug (C_{max}, C_{min}) are a function of the dose, bioavailability, volume of distribution, and rate of metabolism and excretion. Therefore, PK changes affect the antibiotic concentration at the target site and, finally, the clinical outcome.

Volume of distribution

Distribution is the process by which a drug diffuses from the intravascular to extravascular compartments, and it is described by the drug's V_d, that represents the volume of body fluid into which a drug's dose is dissolved. The V_d is important in calculating the plasma half-life ($T_{1/2}$) of a drug, and may also be used to determine the loading dose. The presence of ascites or oedema may necessitate a larger dose, whereas dehydration may require a reduction in the dose.

The V_d is calculated by dividing the amount of drug in the body by the plasma concentration. Usually, highly protein-bound or hydrophilic drugs are found mainly in the vascular compartment and have a small V_d, whereas poorly PPB or lipophilic drugs have a large V_d because they are able to penetrate body tissues.

A V_d of about 0.06 L/kg of body weight corresponds to the plasma compartment, a V_d of about 0.2 L/kg corresponds to the extracellular fluid compartment, and a V_d of about 0.4 L/kg corresponds to the intracellular fluid compartment. If the V_d exceeds the total body water (>0.6 L/kg), the drug is likely sequestered in the intracellular fluid of certain tissues[3].

Clearance

Drug clearance from the body is the result of elimination by renal excretion and by extra renal pathways (no renal clearance), usually by liver metabolism. The unbound moiety of the drug can be eliminated, so an increasing in the plasma level of free drug, commonly observed in critically ill patients, may significantly reduce the clearance mainly for highly protein-bound antibiotics, such as ceftriaxone.

In patients treated with extracorporeal treatment (e.g. RRT), total clearance is the sum of extracorporeal clearance, no renal clearance and residual renal clearance, and this situation further complicate calculations of dose modification.

Half-life

It is common that the rate of plasma clearance is expressed as the time required for the plasma concentration of a drug to decline by 50%, that is the $T_{1/2}$. After rapid IV administration, the decline in plasma drug levels may follow a biphasic curve. The $T_{1/2}$ of the initial phase (alpha-phase $T_{1/2}$) represents distribution of the drug, and the $T_{1/2}$ of the second phase (beta-phase $T_{1/2}$) represents elimination of the drug from the body. The $T_{1/2}$ that is usually reported is the beta-phase $T_{1/2}$. The $T_{1/2}$ remains constant at all times for all drugs that follow first-order kinetics because of concentration decreased, so does the rate of plasma clearance. Drug elimination $T_{1/2}$ is directly related to CL and V_d. It follows that an increased drug CL is likely to reduce $T_{1/2}$, whereas an increased V_d is likely to increase $T_{1/2}$.

$T_{1/2}$ is the pharmacokinetic parameter most changed with renal dysfunction in particular for hydrophilic antibiotics ***(Figure 2)***.

1.2. Antibiotics classification based on physico-chemical properties

Although there are several classification schemes for antibiotics based on bacterial spectrum (broad versus narrow), route of administration (injectable versus oral versus topical), type of activity (bactericidal versus bacteriostatic), or chemical structure, the classification based on their physico-chemical properties is useful in order to predict the dosage adjustment in critically ill patients. The pharmacokinetics of drugs is influenced either by the physico-chemical properties of the molecule, either by the clinical conditions of the patient, that can alter the normal ADME processes.

Furthermore, most sites of infection are extravascular, and their treatment depends on diffusion of the antimicrobial agent out of the bloodstream and into interstitial and intracellular fluid. The ability of a drug to reach the site of infection depends on tissue-related factors (i.e. perfusion to the tissues, surface area of the tissue's vascular bed, existence of tight junctions or capillary pores) and drug-

related factors (such as lipid solubility, molecular size, the drug's pKa, and PPB). An important drug-related factor is the hydrophilicity-lipofilicity balance of the molecule, which is usually expressed by the logP. The logP value of a compound is the 10-base logarithm of the concentration ratios between non-aqueous (octanol) and aqueous (water) phase ($logP_{O/W}$).

Antibiotics can be classified as hydrophilic or lipophilic (hydrophobic) compounds, according to their logP; hydrophilic antibiotics are characterized by low logP values, whereas lipophilic antibiotics are typified by higher values (***Figure 2***). Hydrophilic antibiotics (e.g. Aminoglycosides, Carbapenems, Cephalosporins, Glycopeptides, Penicillins) are characterized by a lower volume of distribution, are unable to cross the plasmatic membrane (with the consequence of inefficacy against intracellular bacteria), and are eliminated mainly by kidneys as unchanged parent drug. Administration of hydrophilic antibiotics in patients affected by impaired renal function requires usually a modification of the dosage regimen in order to avoid toxicity caused by the accumulation of the parent drug or its metabolites.

Lipophilic antibiotics (i.e. Fluoroquinolones, Macrolides, Tetracyclines, Chloramphenicol) are characterized by a higher volume of distribution, are able to cross the plasma membrane (they are active against intracellular bacteria), and are eliminated mainly after liver metabolism.

Physico-chemical properties of antibiotics affect also their clearance during RRT as a consequence of their different distribution in the body, according to the theory that the larger the V_d, the less likely it is that the drug will be removed by RRT.

Hydrophilic compounds, because of their distribution limited to the plasma and to the extracellular space, are promptly and efficiently removed by RRT, so the amount of cleared drug should be carefully evaluated in order to adjust the dosage regimen (during and after the RRT). Conversely lipophilic compounds are able to cross the plasmatic membrane and accumulate in the intracellular compartment, so only a small fraction of the total drug amount present in the body can be removed,

even with a 100% extraction across the RRT filter, so supplemental dosing (during or after RRT) is usually not necessary[4].

The effect of molecular weight (MW) on drug dialyzability is dependent on the type of dialytic membrane and extracorporeal technique. Drug removal is expected to be dependent on MW only if the filter membrane cut-off is lower than the size of the considered drug. This aspect is completely irrelevant for hemofiltration techniques, because almost all antibiotics have MW less than 2000 Da, a value significantly lower than the hemofilter cut-offs, (about 30,000 to 50,000 Da)[5].

1.3. Pharmacokinetic/Pharmacodynamics relationship

Pharmacodynamics (PD) is the study of the biochemical and physiological effects of drugs and their mechanisms of action (***Table 1***).

The major indicator of the effect of the antibiotics is the minimum inhibitory concentration (MIC) that provides information on the susceptibility of the pathogen against the antibiotic. MIC is estimated by different methodologies in the laboratory, and it is defined as the minimum concentration of the antibiotic able to inhibit the growth of the pathogen organism. The use of the MIC as the only marker of the efficacy of antimicrobial therapy has many limits, as the therapeutic goal depends on the interactions between drug concentration at the site of infection, bacterial load, phase of bacterial growth, and the MIC for the pathogen. It follows that a change in any of these factors will alter the activity of the antimicrobial agent against the pathogen and may affect the pharmacological outcome.

Pharmacokinetic/Pharmacodynamics (PK/PD) analysis integrates all this information allowing the clinician to select the optimal antibiotic and dosing regimen for each infectious process and patient, in order to enhance the effect of the antibiotic, minimizing the side effect incidence and the emergence of resistance[6].

The primary PK/PD indices are the following (***Figure 1***):

- Duration of time the plasma concentration of a drug remains above the MIC for a dosing period (T>MIC)
- Ratio of the C_{max} to MIC (C_{max}/MIC)
- Ratio of the AUC during a 24-hour period to MIC (AUC/MIC)
- Post antibiotic effect (PAE), defined as persistent suppression of bacterial growth after a brief exposure of bacteria to an antibacterial agent, even in the absence of host defences.

1.4. PK/PD classification of antibiotics

Regarding to PK/PD relationship, antimicrobials can be categorized by their pathogenic kill characteristics. Understanding these characteristics can aid the clinician in formulating an optimal antimicrobial treatment regimen for an individual patient.

Three major patterns of antimicrobial activity have been described (***Figure 1***)[7,8]:

- Antibiotics with time-dependent killing. The best PK/PD index correlated with efficacy is T>MIC. These drugs have relatively slow bactericidal action and no or short PAEs. This pattern has been described for all of the β-lactam antibiotics, such as penicillins, cephalosporins, and carbapenems.
- Antibiotics with concentration-dependent killing. The best PK/PD index correlated with efficacy is C_{max}/MIC. These drugs achieve increasing bacterial kill with increasing levels of drug. In addition, these agents have an associated concentration-dependent PAE in which bactericidal action continues for a period of time after the antibiotic level falls below the MIC. This pattern has been observed with a large number of antimicrobials including some aminoglycosides and fluoroquinolones, daptomycin and metronidazole.

- Antibiotics with concentration-dependent with time-dependence killing. The best PK/PD index correlated with efficacy is AUC/MIC. These drugs are predominantly bacteriostatic and produce moderate to prolonged PAEs. This pattern is characteristic of tetracyclines, tigecycline, oxazolidinones, and some aminoglycosides and fluoroquinolones.

2. ANTIBIOTICS IN CRITICAL ILLNESS

2.1. Rationale for personalised dosage adjustment in critically ill patients

The management of infection in ICU represents an imperative challenge for critical care clinicians. Useful therapy is based on early recognition of infection and the timely administration of an antimicrobial therapy to combat the contributing pathogens. Moreover, the mortality in this setting remains high, and simultaneous resistance to antibiotics abruptly increases.

At present, antibiotic dosing regimens are derived from studies on healthy volunteers and do not account for these major differences in drug make up. This present approach is likely to lead to suboptimal outcomes for critically ill patients[9].

On the other hand, the critically ill represent a unique population. Critical illness does not have "linear dynamics"[10] of beginning and development: it is characterised by marked homeostatic disturbance, altered end-organ function, variable pre-existing comorbidity, and anthropometric irregularity. Such changes significantly distort the normal drugs PK profile, resulting in drug exposure that is markedly different from the "healthy volunteer"[11].

Furthermore, critically ill patients are treated with combination therapy that can affect the PD/PK antibiotic characteristics. Sometimes they undergo treatments that intuitively could influence the drugs plasma levels (e.g. ECMO or RRT), but very little data is available for this.

Nowadays, the microbial epidemiology of ICU shows an increased prevalence of multidrug resistance (MDR) bacteria, mandating the application of higher antibiotic concentrations for killing bacteria successfully.

Antimicrobial stewardship programs (ASPs) are multidisciplinary programs whose primary aim is to optimize antibiotic use (improve clinical outcomes; minimize the untoward effects of antimicrobial use, and selection of resistant pathogens) in order to reduce ICU length of stay and costs. ASPs usually include several strategies: educational programs, implementation of guidelines, and prospective audit. Interestingly, it also decreases consumption of non-restricted antibiotics. Understanding of the PK/PD changes of antibiotics during CRRT is a relevant part of ASPs[12].

2.2. Impact of critical illness on the pharmacological of antimicrobial agents

Most causes of admission to an ICU (polytrauma, septic shock, severe acute pancreatitis, major surgery) trigger an uncontrolled mediator's cascade leading to pathophysiological changes in haemodynamics, tissue perfusion, and immuno-system competence. In this context, one or more organ failures could occur. These pathophysiological changes are relevant in altering the intra and extra-cellular volume, the synthesis and the plasma levels of the protein or the clearance ability of the organs. Futhermore, they affect the distribution volume (V_d) and the protein binding (PPB) of the clearances (CL) of antimicrobials. The entity of the pharmacokinetic alterations depends on physic-chemical characteristics of antibiotics.

V_d significantly increases in critically ill patients due to expansion from rigorous fluid resuscitation and increased vascular permeability, leading to trans-capillary leakage of fluid and proteins into the extracellular compartment. V_d is also affected by hypoalbuminemia that can have a profound effect on highly albumin bound antimicrobials[13]. Hypoalbuminemia < 25 g/dl is only likely to influence

antibiotic PK when the agent is highly protein-bound (>90%)[14] and mainly eliminated by kidneys (e.g. ceftriaxone, teicoplanin and ertapenem)[13].

As a consequence, the significant expansion of the extracellular fluid may lead to a consistent increase in the V_d of drugs[15]. However, the importance of this extra-volume in affecting drug V_d is different between hydrophilic and lipophilic antimicrobial agents[15].

Hydrophilic compounds (beta-lactams, glycopeptides, lipopeptides, aminoglycosides, azoles as fluconazole or ecchinocandins) are distributed primarily in extracellular space. As such, they present an increased V_d, so that a huge dilution is expected[15].

Conversely, no relevant increase of V_d is expected for lipophilic drugs. In effect, the considerable drug accumulation within the cells, by acting as drugs reservoir, is compensated by passive diffusion for any dilution for lipophilic drugs that can occur in the extra-cellular space[15]. For intravenously administered drugs, the V_d determines the dose (D) needed to achieve the desired plasma concentration (C), in a patient with ideal body weight (IBW):

$$D = C \times V_d \times IBW \quad [1]^{11}$$

The IBW in kilograms can be calculated from the height (H) in inches or centimeters, as follows:

$$IBW\ male = 50 + 2.3(H_{inches} - 60) = 0.9(H_{cm}) - 88 \quad [2]^{2,3}$$

$$IBW\ female = 45.5 + 2.3(H_{inches} - 60) = 0.9(H_{cm}) - 97 \quad [3]^{2,3}$$

For each kilogram of oedema, ascites, or effusion fluid, an additional drug dose may be added to the usual dose (e.g. for aminoglycoside an additional 20 mg may be added to the usual dose).

For antibiotic dosing in the morbidly obese, a similar strategy applies: the dosing weight is the IBW plus 0.4 x (Total body weight - IBW)[16].

In critically ill patients the actual V_d may differ from values obtained from pharmacological tables, and it shows great inter and intra-individual variations. This may increase the error when using V_d in estimating drug dosing. The V_d of aminoglycosides increases approximately 25% in the critically ill, whereas vancomycin, metronidazole, and most beta-lactam antibiotics show near normal values, but with individual variations.

As previously mentioned, critically ill patients have low protein plasma levels. The unbound fraction of the drugs (*fu*) is responsible for the efficacy and toxicity of the molecule[14,17]. *Fu* is the fractions readily available for the clearance by the organ (kidney, liver, and bowel) elimination pathway. Obviously, an increased *fu* results in a larger V_d and a faster renal clearance[14]. On the other hand, critically ill patients often have increased levels of acid α1-glycoprotein[11], which may increase protein binding of some drugs. Thus, the reported unbound fraction in healthy volunteers and in patients with chronic renal insufficiency may differ substantially from the unbound fraction of drugs in critically ill patients. The part of drugs bound to the acid-α1-glycoprotein remains unknown and no data is available in current literature.

Sometimes in critically ill patients, a hyperdynamic state causes an increase in renal (Augmented Renal Clearance, ARC)[14,18,19] or liver (Augmented Liver Clearance, ALC) elimination pathway of the molecules. The ARC is probably caused to increased blood flow, with consequent in Glomerular Filtration Rate[20,21]. The ARC occurrence rate was determined around 15-20% among critically ill patients, even if in subpopulation of this patients it seem to be higher[22].

A clinically useful measure of ARC is a timed urinary creatinine clearance (CLCr). Use of this surrogate is reinforced by observed association between elevated measures ($\geq$ 130 ml/min/1.73 $m^{2)}$ and suboptimal antibiotic concentration for renally eliminated agents[19,23].

ARC has been identified in critically ill patients of a younger age, lower scores of illness severity, and with clinical conditions where an increased cardiac index (CI) has been observed (pregnancy, anaemia, "hyperdynamic phase" of septic shock)[19].

On the other hand, plasma creatinine-based equations such as the Cockcroft-Gault, Modification of Diet in Renal Disease (MDRD) and chronic kidney disease revealed limited accuracy, particularly in patients manifesting ARC[23].

In the setting of the antimicrobial dosing regimens, the physiochemical aspects of the drugs and the pathological changes of the critical illness affect the types of administration.

As previously mentioned, the LD is the quantity of drugs employed to ensure the quick and efficient achievement of the therapeutic concentration target (TCT).

This is the product of the effective plasma concentration and the apparent V_d. After a single intravenous bolus, the concentration plasma levels decrease over time as a consequence of drug distributions. Consequently, in a critically ill setting, where there is a larger V_d than in healthy volunteers, a standard dose results in the failure of the achievement of TCT.

The LD of a given drug is influenced only by its V_d and not by its CL because the LD depends exclusively on the body's compartments where it is spread out, and not on the capacity of elimination of each organ, like the kidneys and the liver. In agreement with this concept, the LD for a given drug has to be calculated irrespective of renal and/or hepatic function[15,24].

Consequently, the LD should be increased for hydrophilic antimicrobials where the clinical conditions caused a more expanded V_d, in order to achieve the TCT. For example, the extracellular fluid is the V_d of aminoglycosides and includes oedema, ascites, and effusion fluids. A standard per-kilogram LD would be inadequate in patients with these conditions, so the amount of excess extracellular fluid should be estimated and the dose increased accordingly. Alternatively, extracellular volume depletion reduces the aminoglycoside V_d[15], and a standard per-kilogram LD

would be excessive. This may explain the increased incidence of aminoglycoside nephrotoxicity in obese patients, who have a reduced fraction of total body weight that is extracellular water[3]. In addition to the nature of the infection (site, medical versus surgical therapy, life-threatening versus less serious), the suspected organism and its MIC should be considered. For example, *Pseudomonas Aeruginosa* has an MIC for gentamicin or tobramycin that is usually less than 2 mg/L. If a ratio of 10 times the MIC is desired for efficient *Pseudomonas a.* killing, a peak concentration of 10 to 20 mg/L will be required.

On the other hand, in critically ill patients the lipophilic antimicrobials do not have a relevant enlargement of V_d, because, as previously mentioned, the extent of drug accumulation within cells, may promptly compensate the passive diffusion due to any dilution of lipophilic antibiotics. This is especially true for those antibiotics which present the largest intrinsic V_d, like tigecycline. Accordingly, there is no rationale for increasing the LD of lipophilic antimicrobials in critically ill patients[15].

The right LD permits adequate plasma concentration in a short time. The MD must be calculated in order to maintain the optimal patient exposure over time. In contrast with LD, the DMD is mainly dependent on the drug CL. Whenever the elimination pathway of a given drug is altered in critically ill patients, the MDs become significantly different from the standard ones[15]. In this setting, a continuous evaluation of the elimination pathways from the organs is mandatory to avoid a failure of the TCT achievement or the toxicity of the drug. The daily assessment of organ functions is necessary in order to prevent an eventual alteration in drug clearance.

The Therapeutic Drug Monitoring (TDM) would be the best tool to target the right LD and MD in critical illness. Nevertheless, this method often has a narrow spectrum of utilisation, in order to prevent the toxicity of some nephrotoxic antibiotics. TDM is used worldwide with aminoglycosides and glycopeptides to ensure appropriate exposure and minimize the incidence of toxicity, whereas

TDM use is unusual in targeting the right dose for the other antibiotic classes, even though recent studies have assessed its usefulness in critically ill patients[19].

For “empirical” dosing, that is in absence of TDM, the PK/PD models are imperative for each antimicrobial agents[19,25].

3. IMPACT OF ACUTE KIDNEY INJURY ON PHARMACOLOGICAL CHARACTERISTICS OF ANTIMICROBIAL AGENTS

3.1. AKI without CRRT: drug dosing adjustment

Total body clearance of an antimicrobial agent is the sum of clearances from different sites in the body, which may include hepatic, renal, and other metabolic pathways. In general, hydrophilic agents are cleaned by the kidney and lipophilic drugs are not renally cleared. Some notable exceptions to this general rule may exist. Ceftriaxone and oxacillin, although hydrolifilic molecules, are cleaned by biliary elimination. Opposite, levofloxacin and ciprofloxacin, although lipophilic, are renally cleared[26].

The amount of renal clearance on the total body clearance is the major factor in the dosing adjustments in renal failure. If the renal clearance of a drug is normally less than 25–30% of total body clearance, impaired renal function is unlikely to have a clinically significant influence on drug removal[11].

The most universal pharmacokinetic equation is :

$$T_{1/2} = 0.693 \times V_d/CL \; [4]^2$$

Because $T_{1/2}$ is reciprocal to the clearance, an interpolation for any degree of renal impairment can be made from the extreme values for normal kidney function and anuria.

Neither renal failure nor extracorporeal blood purification (ECBP) therapy requires adjustment of the LD, which depends solely on V_d. Maintenance doses for drugs that undergo considerable renal excretion should be adapted to the reduced renal clearance, however. Two different approaches are used in adjusting drug dosage in accordance with degree of impairment of renal function in patients that do not do dialysis: the Dettli's rule and the Kunin's rule. [27,28] Dettli's proportional dose reduction rule adjusts the maintenance dosage in proportion to the reduced clearance. Alternatively, Kunin's half-dosage rule is derived from the elimination $T_{1/2}$. The normal starting dose is given, and one half of the starting dose is repeated at an interval corresponding to one $T_{1/2}$. The Dettli's rule results in an AUC that is the same as in normal subjects. With the Kunin's rule, the peak levels (C_{max}) are identical, but the AUC and the C_{min} are higher than in normal subjects[28].

Hydrophilic antimicrobials are mostly renally cleared by glomerular filtration and tubular secretion[29]. Decreased clearance of these drugs is well described in renal dysfunction, and as dose reductions (in time-dependent antimicrobials) or extended dosing intervals (in concentration dependent antimicrobials) are required to prevent drug accumulation and toxicity[29].

Early diagnosis of AKI and assessment of renal function are mandatory for daily dose adjustment of hydrophilic antibiotics. This task is not easy: the creatinine clearance in patients with highly reduced renal function overestimates the glomerular filtration rate (GFR) because of the increased contribution of tubular excretion. The estimations of creatinine clearance (CrCL) as a surrogate GFR using formulas such as Cockroft-Gault and Modified Diet in Renal Disease (MDRD) are widely utilised, but results must be interpreted carefully in critically ill patients[29]. In effect, its application in critical illness has been questioned, because MDRD has not been validated yet in this setting[29]. In critical illness plasma creatinine concentrations can be altered for several reasons, from the worsening of renal function to a persistent catabolic state. In this context, these formulas may result to an inexact estimation of GFR and consequently may conduct to inappropriate dose

adjustments. Therefore, in critically ill patients it would be preferable to calculate urinary CrCL at least once daily in order to estimate GFR[18].

Moreover, some antibiotics, such as aminoglycosides, have a narrow therapeutic window. In this case, dose adjustments are imperative to prevent toxicity that can produce additional nephrotoxicity, and may cause a greater antibiotic accumulation. A vicious circle of injury may start in the already damaged kidney.

Antibacterial and antifungal drugs possess an intrinsic nephrotoxic potential, which is mostly dose dependent for drugs inducing crystal formation and for drugs that act directly on tubular cells or on intra-renal hemodynamic. Prolonged duration of treatment increases the nephrotoxicity of aminoglycosides and amphotericin. Once-daily dosing is effective and actually less toxic than multiple daily doses, because several drugs have a proximal tubule saturable uptake. The rate of administration is important for drugs that cause crystal-induced nephropathy. Amphotericin infusion over 45 minutes did not induce more nephrotoxicity than an infusion over 4 hours, and a continuous infusion appeared to be safer than a 4-hour infusion. The nephrotoxicity of amphotericin B is related to renal vasoconstriction and direct tubular damage by deoxycholate, which is used as a solubilizing agent. Specific drug combinations may result in synergistic nephrotoxicity, such as certain cephalosporins and aminoglycosides, the combination of vancomycin and amino-glycosides, or the combination of cephalosporin and acyclovir.

When the dose reduction due to impaired renal function is mandatory, it is essential to consider antibiotic pharmacodynamics to ensure that targets are still attained by avoiding the toxicity. For instance, for time-dependent antibiotics, an appropriate strategy should be the dose reduction rather than to modify the frequency of administration in order to preserve the T/ MIC[29]. For concentration-dependent drugs, a right LD permit to reach the peak concentration required for optimum bacterial killing. In this setting, the better strategy is to prolong the interval between the doses[29].

However, despite these theoretical recommendations, uncertainty is always present when prescribing antibiotics in patients with multiple organ dysfunction syndrome (MODS) because organ function is very likely to fluctuate. It follows that TDM is again a useful tool to titrate antibiotic dosing in MODS.

Effectively, The Surving Sepsis Campaign Guidelines recommended that the MD of renally cleared antimicrobials are reassessed daily in critically ill patients in order to improve efficacy and /or to avoid toxicity risk[30]. Considering that hydrophilic drugs are usually excreted unchanged by the kidney, whereas the lipophilic ones are usually bio transformed by the liver, to specify the right MD, similar to what happens for the LD in critically ill patients, it is more relevant for hydrophilic antimicrobials than for the lipophilic ones[15].

Drug dosing adjustments can be performed by reducing the dose according total clearance decrease. For the anuric patient this makes:

$$D = D_N \times CL_{ANUR}/CL_N \; [5]^{11}$$

Where D_N is the normal dose, CL_{ANUR} is drug clearance in anuric patients, and CL_N is normal drug clearance. CL_{ANUR} and CL_N are retrieved from pharmacological tables.

On the other hand, published tables or software exist where the empirical doses are listed on the basis of CLCr[31] (T***ables 2 and 3***).

In many clinical settings, the need for a potentially nephrotoxic treatment outweighs the risk of causing kidney dysfunction. In these situations, measures are required to prevent or at least minimize drug-induced renal damage. General preventive measures for nephrotoxicity include addressing all the previously mentioned risk factors that can be corrected or modified. Besides correct dosing and reassessment of concomitant medications, ensuring adequate hydration is of utmost importance before the administration of nephrotoxic drugs[32]. The evidence for preventive hydration is mostly from observational studies, but it is questionable whether more rigorous studies

will ever be conducted. The importance of hydration has been shown for amphotericin, and for drugs that cause crystal-induced nephropathy. Sodium administration is useful to prevent amphotericin B nephrotoxicity[33]. Intervention on urinary pH with urinary alkalinisation may reduce crystal precipitation of some drugs such as sulfadiazine, whereas acidification reduces indinavir precipitation[34].

3.2. AKI needing CRRT

When kidney clearance is the predominant elimination pathway of the given drug, RRT/CRRT causes a substantial removal of the drug and dosing adjustments are frequently required.

Obviously, if its renal clearance is less than 20%[11,26], CRRT will have little influence on total body clearance and dosing adjustments do not have to be considered. Nevertheless, during hepatic failure, the extent to which CRRT contributes to total body clearance may increase, and dose adjustments may become necessary.

As happens in kidney clearance, there are other drug properties affecting clearance by CRRT: V_d, PPB and the resulting *fu*, MW, and drug charge. Only the unbound fraction of a drug is available for filtration, and drugs with a high protein binding are poorly cleared by CRRT. Many factors may alter the fraction of unbound drug such as systemic pH, heparin therapy, hyperbilirubinemia, plasma concentration of free fatty acids, relative concentration of drug and protein, as well as the presence of uremic products and other drugs that may act as competitive displacers[11].

Drug charge affects clearance by the Gibbs-Donnan effect. The Gibbs-Donnan effect may have a significant effect on polycationic drugs[11,35]. Because large anionic molecules such as albumin do not pass through membranes readily, and retained proteins on the blood side of the membrane make the membrane negatively charged, they may partially retard the transmembrane movement of

polycationic drugs (e.g., aminoglycosides). This drug charge and membrane interaction may explain in part the discrepancy between plasma protein binding and observed sieving coefficient (SC).

A large V_d reflects a drug that is highly tissue bound, and consequently only a small proportion actually resides in the vascular compartment available for clearance by endogenous or extra-corporeal routes.

The larger the V_d is, the less the drug will be removed by RRT. A drug with a small V_d ($\leq 1 L x Kg^{-1}$) is more likely to be cleared by extracorporeal therapies than a drug with a large V_d ($\geq 2\ L x Kg^{-1}$). However, there is a significant difference between IHD and CRRT[35,36]. A drug with a large V_d and high clearance during high-flux IHD will rapidly be removed from plasma, but only a small amount of the body's drug content is removed during one dialysis session, and plasma concentration will be restored between therapies. CRRT by its continuous and slower action has much less influence on plasma concentrations of drugs with large V_d, because there is time for continuous redistribution of the drug from the tissues to the blood. Although drug elimination during CRRT is much slower for drugs with large V_d than for drugs with small ones, the same is true for endogenous (hepatic) elimination which has to clear the same V_d. As a consequence, drug dosing adjustments to be made during CRRT are much more dependent on the relative contribution of CRRT to total body clearance of the drug than on the drug's V_d[5].

Most drugs have a MW $\leq$ 500 Da, and very few are greater than 1500 Da (vancomycin at 1448 Da). Conventional dialysis membranes favour dif*fu*sive clearance of low molecular weight solutes below 500 Da, whereas the typical high-flux membranes used for CRRT have larger pores (20 000– 30 000 Da), making no significant filtration barrier to unbound drugs[5,11].

As mentioned previously, the total body clearance of an antimicrobial agent is the sum of clearances from different sites in the body and in case of patients needing CRRT, the amount of clearance of the extracorporeal therapy should be taken into account[37,38]. ECBP elimination, measured as frac-

tional extracorporeal clearance (Fr_{EC}), is considered clinically significant if its contribution to total body clearance exceeds 25% to 30%, is:

$$Fr_{EC} = CL_{EC}/(CL_{EC} + CLnr + CLr)\ [6]^{37,38}$$

Where CL_{EC} is extracorporeal drug clearance, CLnr is non-renal drug clearance, and CLr is renal drug clearance. This also explains why ECBP elimination will not be clinically relevant for drugs with predominantly non-renal clearance. Although it often is difficult to estimate residual renal function (RRF) in ARF, such remaining function also needs to be taken into account in determining total body clearance. Moreover, significant RRF reduces the fraction that is removed by ECBP procedures, which may render ECBP elimination negligible.

Of note, ECBP elimination replaces only glomerular filtration. By contrast, CLr includes glomerular filtration, tubular secretion, and reabsorption. Therefore, any attempt to determine the extracorporeal creatinine clearance using the same dosage guidelines as in patients with reduced renal function cannot be recommended, especially with drugs largely eliminated by tubular secretion.

As a general rule, the efficacy of the drug removal by different techniques is expected to be CVVHDF > CVVH >IHD[26], but indeed CL_{CRRT} may vary greatly, because it depends on the physico-chemical characteristics and the PK behaviour of each single compound.

Drugs significantly cleaned during CVVH or CVVHDF, need to increase the dose regimen in comparison with renal failure or even IHD. The approach taken depends on the type of antimicrobial activity (time or concentration dependent antimicrobial).

For time-dependent antimicrobials the time during which concentrations are maintained above the MIC of the etiological agent (T>MIC) is the most relevant PD parameter. In this regard, it is necessary to ensure that the C_{min} is four or five times that of the MIC. According to this issue, the

best approach is to maintain the frequency of drug administration, modifying the amount of each single dose.

Conversely, for concentration-dependent antimicrobials the most important PD parameter is the ratio between the C_{max} and the MIC, with excellent exposure when C_{max}/MIC ratio is more than 8-10 and when AUC/MIC is > 100. Accordingly, to optimise efficacy with these agents during CRRT, it may be more useful to extend the dosing interval while maintaining a fixed dosage[24]. Accordingly, to optimise efficacy with these agents during CRRT, it may be more useful to extend the dosing interval while maintaining a fixed dosage[24].

If CRRT contributes significantly to the total body clearance of a drug, a supplemental dose, corresponding to the amount of drug removed by CRRT, should be administered, making from equation 5:

$$D = D_N (CL_{ANUR} + CL_{CRRT})/CL_N \quad [7]^{11}$$

Where CL_{CRRT} is the CRRT drug clearance.

Clearance by CRRT can be measured and is :

$$CL_{CRRT} = Q_E \times C_E/C_P \quad [8]^{11}$$

Where, C_E and C_P are drug concentrations in effluent fluid and plasma, respectively. Q_E is the effluent flow rate which is the sum of ultrafiltration flow rate (Q_{UF}) and dialysate flow rate (Q_D). Substitution into the above equation makes:

$$D = D_N (CL_{ANUR} + Q_E \times C_E/C_P)/CL_N \quad [9]^{11}$$

For most drugs, measurements are not available, and CRRT clearances have to be estimated. The sieving coefficient (SC) of a drug is the concentration in ultrafiltrate (C_{UF}) divided by the concentration in plasma, making:

$$SC = C_{UF}/C_P \quad [10]^{11,39,40}$$

The exact formula for the sieving coefficient is $SC=2C_{UF}/ (C_{Pin} + C_{Pout})$, but the differences between C_{Pin} and C_{Pout} are negligible, making the above equation almost correct.

Of note, drug protein binding is the main determinant of SC and it has been suggested that SC can be estimated from published values of protein binding, such that SC= 1 - PPB[40,41]. Measured SC and SC estimated from published values of PPB are correlated. However, as discussed below, PPB in the critically ill is variable and for some drugs SC varies widely (e.g. levofloxacin). Furthermore, SC may be affected by membrane material, drug-membrane interaction, and flux proprieties. Finally, for readily filterable molecules C_{UF} approximates the concentration of unbound drug in plasma, and Sc can be estimated by the unbound fraction (f_u) of the drug, making:

$$CL_{CRRT} = f_u \times Q_{UF} \quad \text{or} \quad CL_{CRRT} = f_u \times (Q_{UF} + Q_D) \; [11]^{11}$$

During CVVH or CVVHDF, respectively. The value of f_u is retrieved from pharmacological tables, but as outlined above, the unbound fraction in the critically ill may differ from these values. CRRT performed in different mode (e.g. a pre-dilution/post-dilution) mode) are explained item by item in the 4th and 5th paragraphs.

4. PRINCIPLES OF DRUG REMOVAL DURING RENAL REPLACEMENT THERAPIES : TECHNICAL FACTORS SPECIFIC TO EXTRACORPOREAL BLOOD PURIFICATION THERAPY

4.1. Membrane

Drug clearance is directly proportional to the surface area of the dialytic membrane or haemofilter, which usually is in the range of 0.5 to 2.0 m2. The pore size of the filter is the other crucial factor determining the extent of drug removal: the cut-off of the modern synthetic dialysis membranes (called high-flux dialytic membranes)is significant larger than that of the old cellulose or

cuprophane membranes (< 1000 D).The modern membranes usually are made up of bio-synthetic material. (polysulfone, polyacrylonitrile, polyamide) with relatively larger pore sizes (5000 to 20,000 D). This means that high MW may protect some large molecules (e.g. glycopeptides) from removal when using old cuprophane membranes, whilst this does not occur when using high-flux dialytic membranes. Conversely, drug removal by haemofiltration doesn't depend on molecule size, considering that all antimicrobial agents have MW lower than the haemofilter's cut-off (20,000 to 50,000 D).

4.2. Diffusion (Haemodialysis)

The efficiency of solute removal based on diffusion in haemodialysis is determined by the concentration gradient, in addition to the porosity and surface area of the dialytic membrane. Compared with convective clearance, diffusive clearance will decrease as MW increases. Owing to the lower diffusive permeability, greater influence of MW on diffusive clearance is found with conventional dialysis membranes than with the synthetic membranes used in CRRT. Diffusive clearance varies between the filter membranes and are greater for polyacrylonitrile (PAN, AN-69) than for polyamide.[42]

In CVVHD, the counter-current flow of dialysate is always considerably smaller than blood flow, resulting in complete equilibration between blood plasma and dialysate. Therefore, the dialysate leaving the filter will be 100% saturated with at least the small, easily diffusible, solutes. Diffusive clearance of small unbound solutes will equal to Q_D. Dialysate saturation (Sd) represents the capacity of a drug to diffuse through a dialysis membrane and saturate the dialysate and is calculated by dividing drug concentration in the dialysate (Cd) by its plasma concentration (Cp):

$$Sd = Cd/Cp \quad [12]^{35,39,40}$$

Consequently, diffusive drug clearance (CLHD) is calculated by multiplying Q_D by Sd:

$$CL_{HD} = Q_D \times Sd \; [13]^{35,39,40}$$

Because either a higher molecular weight decreases the speed of diffusion or a higher Q_D decreases the time available for diffusion, an increase in each of them will give rise to a decrease in Sd.

Sd can theoretically be influenced by drug-membrane interactions and by protein adsorption to the membrane. When extracorporeal drug clearance is calculated, Sd can be approximately replaced by the unbound fraction. Of note, however, Sd does not remain constant, and a serious error would result if the same Sd were used in different Q_D flows[39].

4.3. Convection (Hemofiltration)

Convective solute removal used in hemofiltration is not affected by MW up to the sieving cut off value of the membrane. Continuous hemofiltration usually uses highly permeable membranes, with high cut off values (20,000 to 50,000 D). Because most drugs fall in the lower- to middle-molecular-size category, molecular weight will have little impact on drug sieving with haemofiltration. The capacity of a drug to pass through the membrane of a haemofilter is expressed mathematically in the SC term, which is the relation between drug concentration in the ultrafiltrate (Cuf) and in plasma (Cp).

$$SC = Cuf/Cp \; [10]^{11}$$

For most antimicrobials, SC can be estimated by the extent of the unbound fraction (SC ≈ *fu*). Moreover, an excellent correlation was found between SC and the unbound fraction. SC is a dynamic parameter, however, and is dependent on the age of the membrane and the filtration fraction (Q_{UF}/Q_B, where Q_B is the blood flow rate). A loss of SC will be approximately 20% for drugs such as vancomycin after use of the membrane over 12 hours. Given a Q_B of 100 mL/minute, an increase in Q_{UF} from 14 mL/minute to 28 mL/minute will decrease the SC for drugs like vancomycin by approximately 30%.

There are two basic dilution modes (pre and post dilution) for the substitution fluid, which may influence the solute removal efficiency. In the post dilution mode, the convective clearance of an antimicrobial agent (CLpost-HF) can thus be easily obtained by multiplying Q_{UF} by its SC:

$$\boldsymbol{CL_{post\text{-}HF} = Q_{UF} \times SC \ [14]}^{35,39,43}$$

If haemofiltration is used in pre dilution mode, however, the drug concentration in the plasma entering the haemofilter is diluted by replacement fluid, so the drug clearance will be lowered by a correction factor (CF) determined by blood flow rate (Q_B) and pre dilution replacement rate (Qrep). Drug clearance in pre dilution mode can be calculated:

$$\boldsymbol{CL_{pre\text{-}HF} = Q_{UF} \times SC \times CF \ [15]}^{35,39}$$

Where $CF = Q_B / (Q_B + Qrep)$[35].

Thus, the point of dilution is only likely to significantly affect clearance if the rate of fluid replacement is high. This may partially explain the discrepancy between an in vitro study that failed to demonstrate a clinically significant effect of point of dilution[35] and an in vivo study that revealed a clinically significant reduction in clearance during pre dilution CVVH. In addition, the ratio of pre dilution: post dilution influences SC as well as clearance. For vancomycin, SC steadily decreased as the proportion of pre-dilution decreased. It is evident from the above equations that clearance by CVVH is proportional to the ultrafiltration rate, and therefore dosing needs to be altered with changes in the ultrafiltration rate[35,44]. As the expected magnitude of change in ultrafiltration is substantially greater than the variability of SC, ultrafiltration is the more important consideration.

4.4. Combination with Diffusion and Convection (Haemodiafiltration)

In haemodiafiltration, solutes are removed by both diffusion and convection. The calculation of drug clearance during this combination therapy is extremely difficult, especially at different Q_{UF}

and Q_D rates. Drug clearance with CVVHDF (CLHDF) in the post dilution phase may be estimated by calculating the convective clearance and diffusive clearance from the following equation:

$$CL_{HDF} = Q_{UF} \times SC + Q_D \times Sd \quad [16]^{35}$$

Greater overestimation will result if Sd is replaced by the unbound fraction. It was measured the extracorporeal clearance of several antimicrobials during continuous haemodiafiltration with a Q_{UF} of 400 mL/hour and a Q_D of 1 and 2 L/hour.[45] Compared with the calculated clearances based on the unbound fraction reported in healthy volunteers, the results show that the difference between calculated and measured clearance rates is not clinically significant with a low Q_D, but with a high Q_D, the calculated clearance may be overestimated by up to 100%.

Because an interaction between diffusive and convective solute transfer has been demonstrated in intermittent high-flux haemodiafiltration by protein layer formation on the blood side of the capillary, it also gives the possibility for the two processes to interact in such a manner in CVVHDF that solute removal is significantly less than what would be expected if the individual components were simply added together. In CVVHDF, as the presence of convection-derived solute in the dialysate decreases the concentration gradient, the driving force for diffusion, the Sd, can be lowered even further. The diffusive clearance of a drug during CVVHDF is difficult to predict and will depend on its MW, Q_B, Q_D, and Q_{UF} and the membrane used.

In order to not overestimate the CLHDF, recently Choi et al. proposed:

$$CL_{HDF} = (Q_{UF} + Q_D) \times Sd \quad [17]^{35}$$

4.5. Adsorption to Membrane

Adsorption to filter membranes leads to increased drug removal from plasma and the various filters have different adsorptive capacities. Some membranes such as polyacrylonitrile (PAN) may adsorb

a substantial amount of drugs to their surface[28]. For example, Kronfol and Tian et al. found that PAN membranes have a high adsorbent capacity to bind aminoglycosides and levofloxacin. Adsorption is a saturant process, however, so the influence on drug removal will depend on the frequency of filter changes[45]. In general, with filters lasting approximately 18–24 h, adsorption probably has a minor influence on drug removal, but at present, information about the various filters' adsorptive capacity for most drugs is lacking. Filter adsorption is not accounted for in drug dosing guidelines[5]. Adsorption of drugs onto the membrane may lead to a reduction in membrane permeability and filtration rate over time[5]. Although dosing adjustment will not account for adsorption effects, using drug-adsorbing membranes for CRRT is usually not recommended.

This phenomenon is more relevant in extracorporeal therapy based on adsorbent cartridges. These treatments are utilised in different yields where the accumulation of toxic molecules could worsen the clinical conditions (septic shock) or to make up for a failed organ (liver failure). Unfortunately, even if in vitro data cast light on this problem, there is little and only preliminary data.

Page et al. demonstrated in Coupled Plasma Filtration and Adsorption (CPFA) that the polystyrene cartridge may adsorb vancomycin and piperacillin with an effect that limits itself over time[46].

4.6. High volume-High filtration

High-volume CRRT (HV-CRRT), such as HVHF, is increasingly used in septic patients with ARF in the ICU. Nevertheless, the different effects on pharmacological characteristics of antimicrobial removal between HV-RRT and low-volume CRRT (LV-CRRT) have been understated.

Pharmacokinetic experiments have found that many antimicrobials exhibit two and three compartment characteristics. The central compartment is often referred to as the plasma space, whereas the other compartments are peripheral compartments representative of various tissues in the body. In standard LV-CRRT, the rate-limiting step of drug clearance has been Q_D or Q_{UF},

because Q_B greatly exceeds Q_D or Q_{UF} . Consequently, no appreciable rebound occurs after LV-CRRT stops because the drug transfers to the central compartment at least as fast as it is being removed by CRRT. At HV-CRRT initiation, the central compartment becomes rapidly stripped of unbound drug. The rate-limiting step for any further drug removal becomes the rate at which drug can transfer from the peripheral compartments into the central compartment for removal by HV-RRT. As mentioned earlier, an increase in Q_{UF} from 14 mL/ minute to 28 mL/minute will decrease the SC for drugs like vancomycin by approximately 30%. However, as Q_D increased from 8.3 mL/minute up to 33.3 mL/minute, a 30% decline in vancomycin Sd and an 8% decline in urea Sd were seen with use of AN69 hemodiafilters[47]. Available data indicates that doubling Q_D from standard low-volume flows to higher dialysate flows may result in substantially less than a doubling of solute dialytic clearance, particularly for larger solutes. Increasing Q_D (to greater than 2000 mL/hour) should result in decreasing Sd, but the rate of Sd decline is filter-dependent[47].

Therefore, the drug clearance calculation during HV-CRRT is rather complex, and the changed SC and Sd should be further considered.

In the IVOIRE study (High-volume versus standard-volume haemofiltration: a multicentre randomized controlled trial for septic shock patients with acute kidney injury) a total of 140 critically ill patients with septic shock and AKI were randomized to either HVHF at 70 mL/kg/h or standard-volume haemofiltration (SVHF) at 35 mL/kg/h, for a 96-h period. In 45 patients all antibiotics were dosed during 5 days. All antibiotics were given at a standard dosage used in non-AKI patients (i.e. 16 g per day for piperacillin or 2 g per day for ceftriaxone) and at the same dosage in the two groups to avoid bias as recommended by the external reviewers at study acceptance by the authorities.

All antibiotics were easily filtered, and mean sieving coefficients were from 38.70 to 96.70 %. The mean elimination half-life of all the agents in the HVHF group (from 1.29 to 28.54 h) was significantly shorter than that reported in the SVHF group (from 1.51 to 33.85 h)[48].

5. RATIONALE FOR APPROPRIATE DOSAGE ADJUSTEMENT OF ANTIBIOTICS DURING CRRT

In patients with concomitant renal failure on CRRT, underdosing may lead to inadequate antibiotics therapy, with increased mortality risk, whereas overdosing may lead to drug accumulation and unnecessary toxicities. Drug dosing adjustments during CRRT can be guided by using available drugdosing recommendations, by measuring or estimating CRRT drug clearance, or by monitoring drug serum concentrations. Drug-dosing recommendations for patients with ARF receiving CRRT is always in progress with the advances in CRRT technology, the introduction of new extracorporeal therapies in septic shock or organ failure and the selling of new antimicrobial agents. Nonetheless, published drug-dosing recommendations for ARF patients on CRRT are becoming available but still limited. After searching the literature and reviewing recent clinical investigations, we adopted some of these recommendations. Then we summarized the pharmacokinetic characteristics and dosing recommendations of some antimicrobials most commonly used in critically ill patients undergoing CRRT into a complete dosing guide (***Table 3***).

It is widely recognized that the extent of drug removal during CRRT in critically ill patients with ARF is dependent on numerous factors of patient, illness, drug, and the operational modality of CRRT. These parameters vary widely among different patients, or even during the length of stay in the same patient.

CRRT does not always yield stable conditions, because Q_B and Q_{UF} may vary ongoing. Moreover, the renal function and critical illness may reverse under effective treatment during the disease course. Therefore, it is extremely difficult and almost impossible to devise a comprehensive dosing guide for various antimicrobials that encompasses all of the potentially changing variables involved

in CRRT for all patients, as well as for the various combinations of prescriptions, machines, filters, and other variables. Therapy must be individualized to the needs of each patient.

Making these estimates is time-consuming, requiring a careful search for basic pharmacokinetic data.

Based on the understanding of the principles of drug removal by CRRT and the pharmacokinetics of various antimicrobial agents, the drug dosage and dosing interval may be estimated using mathematical equations for application in individualized therapy. Drug clearance must be calculated to determine a maintenance dose. The serum concentration at steady state (Cp_{ss}) multiplied by the CL_{EC} provides the clinician with the amount of drug specifically removed by ultrafiltration per hour under steady-state conditions[28]. Therefore, the amount of drug removed by CRRT (D_{EC}) can be calculated using the following equation:

$$\boldsymbol{D_{EC} = Cp_{ss}\, xCL_{EC}\, X\, T_{dur}[18]^{28}}$$

where T_{dur} is the duration of CRRT.

CL_{EC} can be calculated using Equations 11, 12 to 13, and 14, as shown previously, according to treatment modality. The total amount of drug required during CRRT (D) may be calculated using the following equation, including the typical anuric dose (D_{anur}) in addition to D_{EC}:

$$\boldsymbol{D = D_{anur} + D_{EC} = D_{anur} + Cp_{ss}\, x\, CL_{EC}\, xT_{dur}[19]^{28}}$$

Besides Equation 17, the drug dose during CRRT in an anuric patient also may be estimated using the following equation[45]:

$$\boldsymbol{D = D_{anur}\, x\, [1 + CL_{EC}/CL_{NR}/2(interval/half\text{-}life)]\ [20]}$$

where"*half-life"* is the $T_{1/2}$ of the drug in an anuric non-dialyzed patient and "*interval"* is the dose

interval in an anuric non-dialyzed patient.

At present, there is an increasing tendency to start CRRT earlier in the course of illness, and RRT may contribute to drug clearance. According to Dettli's equation and the related investigation by Keller and associates, the estimated dose during CRRT in a patient with RRT may be calculated as follows[45]:

$$D_{EC} = Dn \times [Px + (1 - Px) \times CL_{CRtot}/CL_{CRn}] \quad [21]$$

Where Dn is the normal dose, Px = CL_{NR}/CL_N (in which CL_N = normal drug clearance), CL_{CRtot} is the sum of renal and extracorporeal creatinine clearance, and CL_{CRn} is the normal creatinine clearance. This equation uses the patient's actual creatinine clearance to estimate drug clearance and drug dosing, and dose estimates will automatically be adjusted as changes occur in renal function[45]. Although complex mathematical models have been proposed, an accurate and usable equation remains unavailable. Most mathematical models are demonstrated to be suitable for use only with certain drugs on a conditional basis; their application in clinical practice is still limited.

In summary, four formulas are proposed on the basis of CRRT modality in following ***Table 4*** [35]:

Modality	***Formula***
CVVH	$D_{CVVH} = Cp_{ss} \times Q_{UF} \times f_u \times I$ $D_{CVVH} = D_N \times [(CL_{NR} + (Q_{UF} \times SC))/CL_N]$
CVVHDF	$D_{CVVHDF} = D_N \times [Px + (1 - Px) \times CL_{CRtot}/CL_{CRn}]$
All modality	$D = D_{anuria} / [1- (CL_{EC}/(CL_{EC} + CL_{NR} + CL_R))]$

C_{pss}, measured blood concentration at steady state; CL_{CRn}, normal creatinine clearance; CL_{CRtot}, sum of renal and extracorporal creatinine clearance; CL_{EC}extracorporeal clearance; CL_N, normal total drug clearance; CL_{NR}, non renal clearance; CL_Rrenal clearance; D_{anuria}, recommended dose for anuric patients; D_N, dose recommended for patients with normal renal function; I, dosing interval; $P_x$extrarenal clearance fraction (CL_{anur}/CL_N); SC, sieving coefficient; fu, unbound fraction; Q_{UF}, ultrafiltration rate.

Whether it may be more appropriate to increase the drug dose or to shorten the dosing interval in critically ill patients during CRRT is dependent on antimicrobial mechanisms of action and the kill characteristics of the various classes of antimicrobial agents. For concentration-dependent kill characteristic antimicrobial agents, it is better to increase the drug dose, because their antimicrobial effects correlate with the C_{max}. For example, low doses of aminoglycosides used in anuric non-dialyzed patients result in low C_{max} with low bacterial killing efficiency, although the risk of toxic adverse effects also is low. A preferable approach, however, is to increase the single daily dose to achieve the higher C_{max} in CRRT, although the minimum (trough) drug concentration (C_{min}) is decreased by CRRT and the risk of side effects is considerably reduced. By contrast, for time-dependent kill characteristic antimicrobial agents such as β-lactam antibiotics, it is better to shorten the drug dosing interval, because their antibiotic effects correlate with T > MIC. The shorter dosing interval during CRRT may be estimated from the following equation, and the individual dose remains unchanged from that used in anuric no-dialyzed patients[45]:

$$Iv_{EC} = Iv_{anu} \times [CL_{NR}/CL_{EC} + CL_{NR})] \quad [22]$$

Where Iv_{EC} is the interval during CRRT and Iv_{anu} is the interval in an anuric patient. Not only are pharmacokinetics and pharmacodynamics often less predictable in critically ill patients, but it also has not been consistently shown that convincing results may be obtained from current drug dosing recommendations or be estimated accurately using available mathematical equations. Therefore, serum drug concentration monitoring is highly recommended whenever possible, especially for those drugs with a narrow therapeutic range. Although the monitoring of total drug concentrations is considered a reasonable strategy to enhance optimal dosing and minimize toxic side effects, it is no readily available for all medications. The following equation often is used to estimate the required dose ($D_{required}$) to achieve the desired peak concentration (C_{max}) from the actual trough (or any) concentration (C_{actual})[45]:

$$D_{required} = (C_{max} - C_{actual}) \times V_d \times \text{Body weight} \quad [23]$$

Among all antimicrobial agents, aminoglycosides and glycopeptides have been studied more than other classes due to their proved nephrotoxicity. Recently, the increasing incidence of Extended-spectrum β-lactamases (ESBLs) or carbapenemase-producing Gram-negative bacteria strains such as emergent linezolid-resistance staphylococci and enterococci boosted to consider the PK/PD relationship to achieve TCT in other antimicrobial classes. Unfortunately, in this field the recent literature is controversial and confirms the absolute variability of critically ill patient in term of PK/PD profiles. In our point of view, TDM represents the best tool to achievement the TCT. Nevertheless, PK/PD modeling and simulation software allow to guide dosing strategy for antibiotics and might be utilized where the TDM is not available.

Although the authors tried to categorize antimicrobial agents, the reality is that nearly all drugs undergo a combination of major, minor, and co-dominant elimination pathways. The authors proposed the adjustment dosage during CRRT, without taking into account the difference in prescribed CRRT dose. Exclusively, the dosage difference related to CRRT modality are shown in the table. The choice was imposed because in the setting of CRRT too much variables highly affect the plasma antimicrobials concentration during CRRT. Effectively, the type of filter, modality and intensity of CRRT, pre-dilution or post-dilution modality, partial preserved renal clearance, the adsorption by the membranes, and the addiction of adsorption techniques (e.g. cartridge of polystyrene resins) affect the drug plasma levels during the patient's exposure of the pharmacological treatment. Table 3 limits to suggest the dosage, but the physician should take into account every PK/PD relationship, the breakpoint of the bacteria and the CRRT dose with its changes over time (e.g. decreasing of SC over time, delivery dose, and downtime).

Drugbank, Micromedex, Sanford guide, Lexi-Comp, Epocrates, and other online or mobile databases offer extensively referenced continuously updated and easily available data on an extensive library of drugs[31]. A quick look at the pharmacokinetic or ADME sections of a drug monograph can help the practitioner quickly decide if renal dose adjustment is necessary. Highly

similar drugs in the same class cannot be assumed to share common pharmacokinetics and elimination[31].

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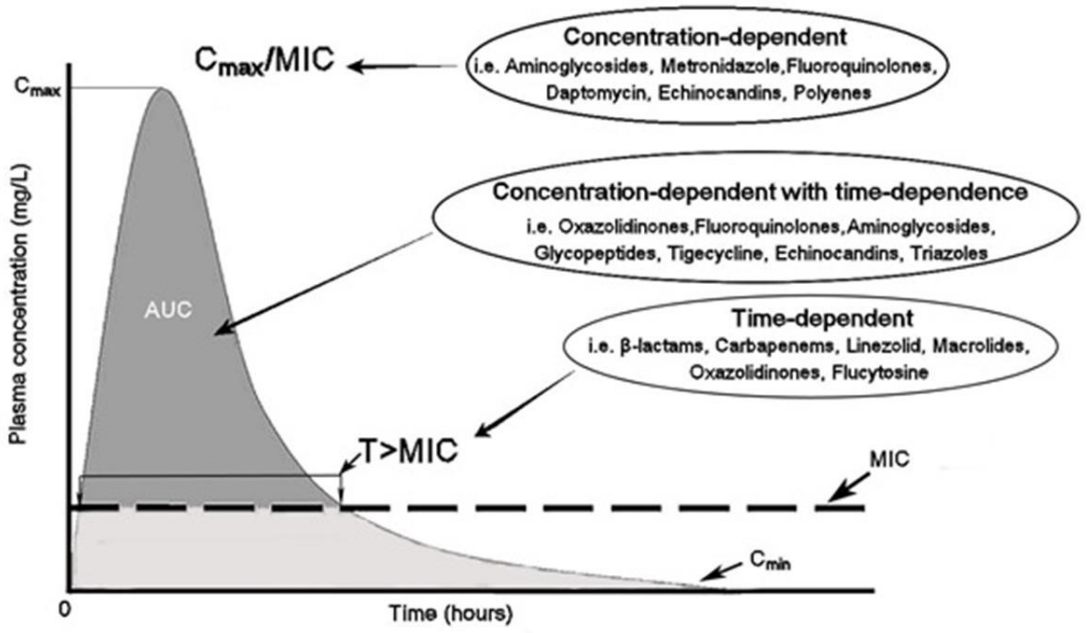
Cmax/MIC
Concentration-dependent
i.e. Aminoglycosides, Metronidazole,Fluoroquinolones,
Daptomycin, Echinocandins, Polyenes
Concentration-dependent with time-dependence
i.e. Oxazolidinones,Fluoroquinolones,Aminoglycosides,
Glycopeptides, Tigecycline, Echinocandins, Triazoles
Time-dependent
i.e. β-lactams, Carbapenems, Linezolid, Macrolides,
Oxazolidinones, Flucytosine
Cmax
Plasma concentration (mg/L)
AUC
T>MIC
MIC
Cmin
0
Time (hours)

Figure 1

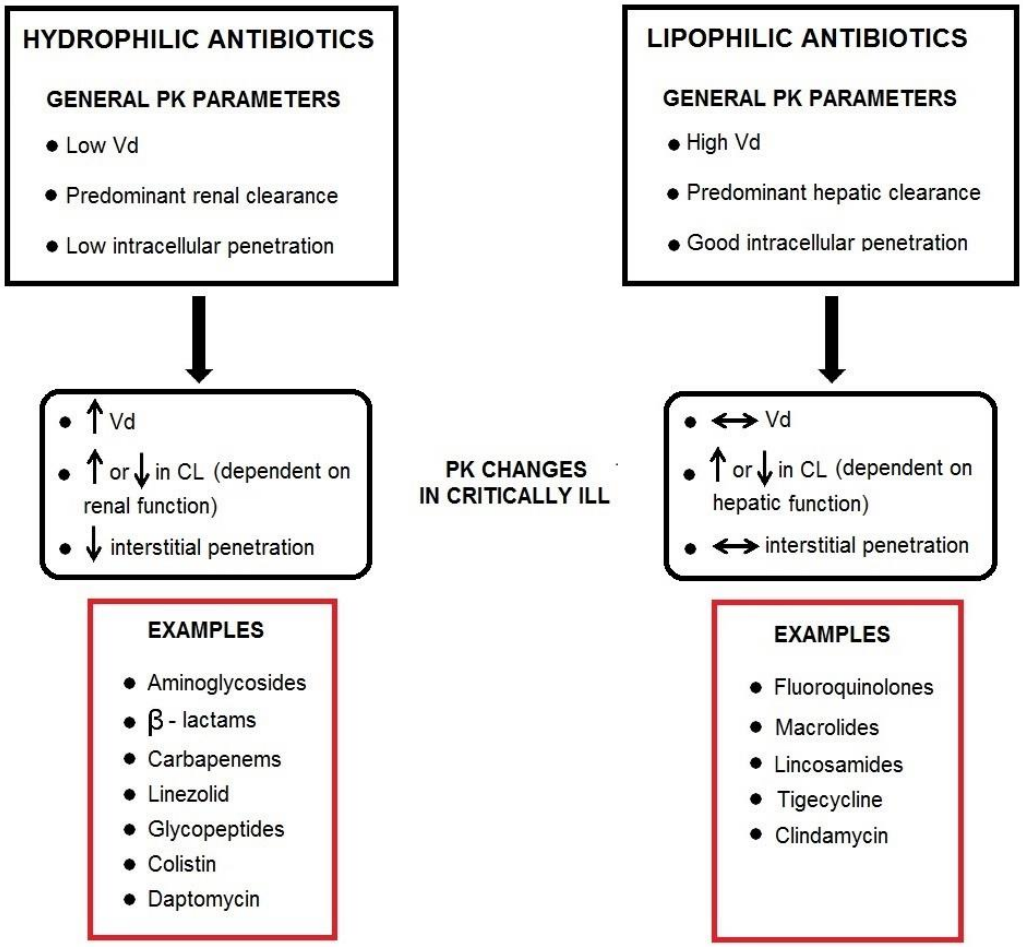
HYDROPHILIC ANTIBIOTICS
GENERAL PK PARAMETERS
Low Vd
Predominant renal clearance
Low intracellular penetration
↑ Vd
↑ or ↓ in CL (dependent on renal function)
↓ interstitial penetration
EXAMPLES
Aminoglycosides
β - lactams
Carbapenems
Linezolid
Glycopeptides
Colistin
Daptomycin
PK CHANGES IN CRITICALLY ILL
LIPOPHILIC ANTIBIOTICS
GENERAL PK PARAMETERS
High Vd
Predominant hepatic clearance
Good intracellular penetration
↔ Vd
↑ or ↓ in CL (dependent on hepatic function)
↔ interstitial penetration
EXAMPLES
Fluoroquinolones
Macrolides
Lincosamides
Tigecycline
Clindamycin

Figure 2

Figure 1. Plasma drug concentration-time profile and pharmacokinetic/pharmacodynamics relationship of antibiotics.

Legend. T>MIC: the time for which a drug's plasma concentration remains above the minimum inhibitory concentration (MIC) for a dosing period; C_{max}/MIC: the ratio of the maximum plasma antibiotic concentration (C_{max}) to MIC; AUC/MIC: the ratio of the area under the concentration-time curve during a 24-hour time period (AUC) to MIC

Figure 2. The interrelationship of hydrophilicity and lipophilicity of antibiotic molecules on the pharmacokinetic characteristics and the changes in critically ill patients.

Legend. CL: clearance; V_d: volume of distribution.

Table 1. Mechanism of Action of Antimicrobial Agent

Antimicrobial Agent Classes	Mechanism of Action
Aminoglycoside Agents	Aminoglycoside agents are irreversible inhibitors of protein synthesis. Inside the microorganism, they bind to specific 30S subunit ribosomal protein.
Beta-Lactam Agentes (Penicillin, Cephalosporin, and Carbapenem)	Beta-lactam are irreversible inhibitors of cell-wall synthesis. Their bacteriostatic effect is related to inhibition of essential enzymes (transpeptidases, carboxypeptidases) involved in peptidoglycan biosynthesis.
Fluoroquinolone Agents	Fluoroquinolone agents are inhibitors of bacterial DNA synthesis. They inhibit bacterial topoisomerase II (DNA gyrase) and topoisomerase IV. This inhibition prevents the relaxation of positively supercoiled DNA is required for normal transcription and replication.
Glycopeptide Agents	Glycopeptide agents are irreversible inhibitors of the bacterial cell-wall synthesis. They bind to acyl-D-alanyl-D-alanine of peptidoglycan.
Lipoglycopeptide Agents	Lipoglycopeptide agents have a multiple mechanism of action. They combined action on the cell wall synthesis and disruption of bacterial cell membrane barrier function. They bind to acyl-D-alanyl-D-alanine of peptidoglycan. In addition, they bind bacterial target called as lipid II present in the cell membrane.
Macrolide Agents	Macrolide agents are agents are irreversible inhibitors of protein synthesis. They bind 50S subunit of bacterial ribosomes, so tRNA translocation remains blocked.
Miscellaneous Agents	
Aztreonam	Aztreonam agent is irreversible inhibitor of cell-wall synthesis. Its effect is related to inhibition of penicillin binding protein 3 (PBP3). By binding to PBP3, aztreonam agent inhibits the third and last stage of peptidoglycan synthesis.

Chloramphenicol	Chloramphenicol agent is irreversible inhibitors of protein synthesis. It binds 50S subunit of bacterial ribosomes, so it prevents protein chain elongation (the peptidyltransferase activity is blocked).
Clindamycin	Clindamycin agent is irreversible inhibitors of protein synthesis. It specifically binds the 23S RNA subunit of 50S bacterial ribosome subunit.
Colistin	Colistin agent is a surface active agent which penetrates into and disrupts the bacterial cell membrane. It is polycationic and has both hydrophobic and lipophilic moieties. It interacts with the bacterial cytoplasmic membrane, changing its permeability. In addition, inside the microorganism, Colistin causes the precipitation of cytoplasmic components, primarily ribosomes.
Daptomycin	Daptomycin agent interferes with activity of the bacterial cell membrane. The binding and integration of Daptomycin into the cell membrane is calcium dependent. It causes rapid depolarisation, resulting in a loss of membrane potential leading to inhibition of protein, DNA and RNA synthesis, which results in bacterial cell death.
Fidaxomicin	Fidaxomicin agent specifically inhibits nucleic acid synthesis by impairing the initiation of RNA chain synthesis and transcription. Its effect is related to inhibition of RNA polymerase activity, so the transcription process remains blocked.
Metronidazole	Metronidazole agent is a pro-drug which is converted inside anaerobic bacteria in its active form by oxredox reaction. The reduced form of Metronidazole covalently binds to DNA, disrupt its helical structure, inhibiting bacterial nucleic acid synthesis.
Trimethoprim	Trimethoprim agent inhibits bacterial DNA synthesis. Trimethoprim binds to dihydrofolate reductase and inhibits the reduction of dihydrofolic acid to tetrahydrofolic acid (Trimethoprim's affinity for bacterial dihydrofolate reductase is several thousand times greater than its affinity for human dihydrofolate reductase).
Oxazolidinone Agents	Oxazolidinone agents are irreversible inhibitors of protein synthesis. They bind to a site on the bacterial 23S ribosomal RNA of the 50S subunit and prevent the formation of a functional 70S initiation complex.
Tetracycline Agents	Tetracycline agents inhibit bacterial protein synthesis by preventing the association of aminoacyl-tRNA with the 30S bacterial ribosome subunit.

Antifungal Agents

Azole	Azole- based antifungal agents are irreversible inhibitors of ergosterol synthesis. They inhibit the 14-α-sterol-demethylase enzyme involved in ergosterol biosynthetic pathway. This inhibition leads to accumulation of 14-α-methylsterols on the fungal surface, which results in arrest of fungal growth.
Antimetabolite (Flucytosine)	Flucytosine agent acts directly on fungal organisms by competitive inhibition of purine and pyrimidine uptake and indirectly by intracellular metabolism to 5-fluorouracil. Inside the fungal cell, Flucytosine is metabolized to 5-fluorouracil, which is extensively incorporated into RNA and inhibits synthesis of both DNA and RNA. It

	also appears to be an inhibitor of fungal thymidylate synthase.
Echinocandin	Echinocandine agents are inhibitors of fungal cell-wall. They inhibit beta-(1,3)-glucan synthase involved in the synthesis of beta-(1,3)-D-glucan, an essential component of the cell-wall.
Polyene (Amphotericin B)	Amphotericin B acts by irreversibly binding to ergosterol in the cell membrane. This creates a transmembrane channel, and the resultant change in membrane permeability allowing leakage of intracellular components.

Antituberculous Agents

Ethambutol	Ethambutol agent inhibits arabinosyl transferases which is involved in cell wall biosynthesis. By inhibiting this enzyme an increase in cell wall permeability occurs.
Isoniazid	Isoniazid agent pro-drug which has to be activated by bacterial catalase. The active form of Isoniazid inhibits the synthesis of mycoloic acids, an essential component of the bacterial cell wall.
Rifampicin	Rifampicin agent acts by inhibition of RNA synthesis. It binds and blocks DNA-dependent RNA polymerase enzyme.

Table 2. Recommended dosing regimen of most frequently renally excreted antibiotics based on renal function (modified by Pea et al.)[49]

	Renal function			
Antibiotic	**Increased (hypoalbuminemia or increased CI)**	**Normal**	**Moderately impaired CLCr 10-50 ml/min**	**Severely impaired CLCr < 10ml/min**
Piperacillin/tazobatam	16/2 g q24h CI or 4/0.5 g q6h EI over 4 hours	4/0.5 g q6h **(ClCr >40 ml/min)**	4/0.5 g q6h* (**CLCr 20-40 ml/min)**	2/0.25 g q6h* **(CLCr ≤ 20 ml/min)**
Ampicillin/sulbactam	3 gm q6h 3	3 gm q6h	3 gm q8-12h	3 gm q24h
Cefotaxime	4 to 6 g q24h CI or 2 g q4-6h	2 g q6-8h	2 g q8-12h	1 g q6-8h
Ceftazidime	4 to 6 g q24h CI	2 g q8h	1 g q8-12h	0.5 to 1 g q24h
Cefepime	4 to 6 g q24h CI or 2 g q8h EI over 3 hours	2 g q8h 6g 24h CI (**CLCr > 60 ml/min)**	2 g q12h or 4g 24 h CI **(CLCr 30-60ml/min)**	2 g 24 h CI (**if CLCr 10-30 ml/min)** 1 g q24h

Imipenem	500 mg q4h or 250 mg q3h over 3 hours CI	500 mg q6h	250 mg q6h	250 mg q12h
Meropenem	1 g q4-6h over 6 hours CI /EI	1 g q6h EI	1g q12h EI **if CLCr 20-50 ml/min**	250 mg q12h EI **If CLCr ≤ 20 ml/min**
Ertapenem	LD 2g Increased frequency of administration (e.g. 1g q12h)	1 g q24h	1 g q24h	500 mg q24h
Gentamycin	9 to 10 mg/kg q24h	7 mg/kg q24h	7 mg/kg q36-48h	7 mg/kg q48-96h
Tobramycin	9 to 10 mg/kg q24h	7 mg/kg q24h	7 mg/kg q36-48h	7 mg/kg q48-96h
Amikacin	25 mg/kg q24h	20 mg/kg q24h	15 mg/kg q36-48h	15 mg/kg q48-96h
Ciprofloxacin	600 mg q12h or 400 mg q8h	400 mg q12h	400 mg q12h	400 mg q24h
Levofloxacin	500 mg q12h	750 mg q24h/500 mg q12h	500 mg q24h **If CLCr 20-49 ml/min**	500 mg q48h **If CLCr ≤ 20 ml/min**

Vancomycin	LD 30 mg/kg MD2-3g CI q24h CI	LD 20 mg/kg 2g CI	1-1,5 g 24h CI	0,5 -1 g 24 CI
Teicoplanin	LD 12 mg/kg q12h for 3 to 4 doses; MD 6 mg/kg q12	LD 12 mg/kg q12h for 3 to 4 doses; MD 4 to 6 mg/kg q12h	LD 12 mg/kg q12h for 3 to 4 doses; MD 2 to 4 mg/kg q12h	LD 12 mg/kg q12h for 3 to 4 doses; MD 2 to 4 mg/kg q24h
Daptomycin	6-8 mg/kg q24h	6 mg/kg q24h	6 mg/kg q24h **If CLCr > 30 ml/min**	6 mg/kg q48h **If CLCr ≤ 30 ml/min**
Metronidazole	500mg q6h	7mg/kg q6h	7mg/kg q6h	7mg/kg q12h
Fluconazole	LD 800mg first day MD 400 mg q24	LD 800mg first day MD 400 mg q24	LD 400mg first day MD 400 mg q24	LD 200mg first day MD 200 mg q24

Table 3. Adjustment of Antimicrobial Regimen for different Drugs in patients with Acute Renal Failure Undergoing Continuous Renal Replacement Therapy (CRRT)

Antimicrobial Agent	MW	LogP	PPB [%]	V_d [L/Kg]	$T_{1/2}$ [h]	T1/2 anuria (h)	Standard Dosage	Dosage Adjustment on CRRT
Aminoglycoside Agents (Concentration-dependent)								
Amikacin	585.6	-3.2	0-11	0.13- 0.29	2- 3	4-82	20 mg/kg q24h	LD 25 mg/kg MD 7.5/kg q24-48 h
Gentamicin	477.6	-1.6	0-30	0.29- 0.37	2	50-70	7 mg/kg q24h	LD 3mg/Kg MD 2mg/kg q24-48
Netilmicin	475.6	-1.4	0-30	0.16- 0.34	1.99-3.2	32-52	2.0 mg/kg q8h	2.0 mg/kg q8h pea
Tobramycin	467.5	-3.0	10	0.26-0.32	2	53	7 mg/kg q24h	LD 3mg/Kg MD 2mg/kg q24-48
Carbapenem Agents (time-dependent)								
Ertapenem	475.52	-0.20	95	0.12	4h	14h	1g q14h	CVVHDF/CVVHD 1g q24h
Imipenem	299.3	-0.19	20	0.14-0.23	1	3	0.5-1.0 g q6h	0.5 mg q6-8 h
Meropenem	383.5	-0.69	2	0.25	1	3.4-20	1.0 g q6hLD EI or 2g q6h	CVVH/CVVHD/CVVHDF 0.5 q6-8h up to 1g q4-6 h (residual CL_R)
Cephalosporin Agents (time-dependent)								
1st Generation								

Cefazolin	454.5	-0.4	74-86	0.14	1.8	40-70	0.5-1.5 g q6-8h	CVVH 1-2g q12h CVVHD or CVVHDF 2g q12h
Cefradine	349.4	0.7	8-17	0.30	0.7-1.3	8-15	1.0g q6h	1g q12h
Cephalexin	347.4	0.55	15-20	0.23-0.35	0.7-1	16	0.5-1 g q6h	0.5g q12h
2nd Generation								
Cefaclor	367.8	0.85	25	0.24-0.35	0.5-1	2-3	250-500 mg q8h	500mg q8-12h
Cefamandole	462.5	-0.05	56-78	0.16-0.25	1	11	0.5-1.0 g q4-8h	1g q18h
Cefoxitin	427.4	0.22	41-75	0.12-0.20	1	13-23	1.0-2.0 g q6-8h	1g q18h
Cefuroxime	424.4	-0.24	50	0.25-0.30	1.4-1.8	17-20	0.75-1.5 g q8h	CVVH 0.5g q8h
3rd Generation								
Cefmenoxime	511.6	-0.13	77-84	0.10-0.35	0.78-1.6	15.6	1.0 g q6h	CVVH Quf 1L/h 1g q24h
Cefoperazone	645.7	-0.11	82-93	0.14-0.20	2.4	2.4	1.0-2.0 g q12h	1-2 g q24h
Cefotaxime	455.5	0.14	27-38	0.25-0.35	0.8-1.4	10-15	2.0 g q6-8h	CVVH 1g q6h
Ceftazidime	546.6	-1.2	5-17	0.28-0.36	1.9	21-23	1.0-2.0 g q8h	1g q8h or 3g/day IC up to 2g q8h 3g q8h for intermediatelyresistent patogenswith MIC8mg/ml
Ceftriaxone	554.6	-0.01	95	0.08-0.3	5.8-8.7	8-16	2 g q12h or 2g q24h	2 g q24h or 2g q 12 h

4th Generation								
Cefepime	480.6	-0.37	16-20	0.33-0.40	2	13.5	2 g q8h 6g 24h CI	1-2 g q12h 2g q8h (residual CL_R)
Cefpirome	514.6	-1.01	10	0.32	1.4-2.3	14.5	2.0 g q12h	1g q12h (werf) 2g q8h

Antimicrobial Agent	**MW**	**LogP**	**PPB [%]**	**V_d [L/Kg]**	**$T_{1/2}$ (h)**	**T1/2anuria (h)**	**Standard Dosage**	**Dosage Adjustment on CRRT**
Fluoroquinolone Agents (concentration-dependent with PAE)								
Ciprofloxacin	331.3	-0.57	20-40	1.2-2.7	3-6	8.7	400 mg q6h	400mg q12-24h
Enoxacin	320.3	-0.97	40	2	4-6	30	200-400 mg q12h	400mg q24h
Levofloxacin	361.4	-0.02	24-38	1.25	6-8	40	750 mg q24h 500mg q12h	LD 0.5 mg/die MD 0.25 g q24h or 0.5 g q48h 0.5 g q24h residual CL_R or Q_{UF} > 3 L/h
Moxifloxacin	401.4	0.01	30-50	1.7-2.7	11.5-15.6	12	400 mg q24h	400 mg q24h
Ofloxacin	361.4	-0.02	20-32	2.4-3.5	5-10	40	400 mg q12h	400mg q8h

Pefloxacin	333.4	0.2	20-30	1.5-1.9	7-14	8.5-15	400 mg q12h	400-800mg q24h
Glycopeptide Agents (time-dependent with PAE)								
Teicoplanin	1877,7-1879.7-1893.7	1.74	>90	0.9-1.6	88-140	157-567	LD 12 mg/kg q12h for 3 to 4 doses; MD 4 to 6 mg/kg q12h	LD 6mg/kg q12 for 3-4 doses, MD 3-6 mg/kg q24
Vancomycin	1449.2	1.11	55	0.7	4-6	180	2g CI	LD 15-20 mg/kg mg/kg MD 0.5 q12h H-HF 1g q12h
Ramoplanin	2554.1	1.7	minimal systemic absorption following oral administration	minimal systemic absorption following oral administration	3.8	ND	200-400 mg q12h	NA
Lipoglycopeptide Agents (time-dependent, concentration-enhanced, with PAE)								
Dalbavancin	1816.7	3.58	93-99	0.1-0.19	204-346	376	Single dose 1500 mg/ 1000 mg + 500 mg 1 week later	NA
Oritavancin	1793.1	1.92	85	1.25	245	ND	Single dose 1200 mg	NA (vitro study)

Telavancin	1792.1	2.32	90	0.14	7-9	ND	10 mg/kg q24h	NA (vitro study)
Macrolide Agents (time-dependent)								
Clarithromycin	748.0	3.18	50-70	3	3-7	4	500 mg q12h	500mg q12h
Erythromycin	733.9	2.37	75-95	0.75	0.8-3	5.4	250-500 mg every 6 hours	NA
Azitromicina							500mg q24h	500mg q24h
Miscellaneous Agents								
Aztreonam	435.4	0.04	56	0.1-0.2	1.6-2.9	8.4	1.0-2.0 g q8-12h	CVVH 1.0-2.0 g q12h CVVHDF CVVHD 2g q12
Chloramphenicol	323.1	1.15	50-60	0.5-1	1.6-3.3	3-7	12.5-25 mg/kg q6h	NA
Clindamycin	425.0	1.76	60-95	0.6-1.2	2.4	4	600 mg q6-8h	600mg q6-8h
Colistin	1634.9	-1.23	50	0.34	9	13	LD 9 million U MD 4.5 million U q12h	CVVH LD 9 million U MD 4.5 million U q12h CVVHDF LD 12 million U 6.5-7.5 million U q12h
Daptomycin	1620.7	-0.47	90-93	0.1	8	30	4-6 mg/kg q24h	4-6mg/Kg q48h

Fidaxomicin	1058.0	5.59	minimal systemic absorption following oral administration	minimal systemic absorption following oral administration	11.7	ND	200 mg q12h	NA
Metronidazole	171.1	-0.15	<20	0.55	6-14	7-21	7.5 mg/kg q6h	7.5 mg q6h
Trimethoprim	290.3	1.26	42-46	0.7-1.5	8-11	24-30	100-200 mg q12h	100-200mg q12h
Trimethoprim/ (Sulfamethoxazole 1:5)	290.3 (253.3)	1.26 (0.79)	42-46 (70)	0.7-1.5 (0.3)	8-11 (10)	24-30 (80)	2.5–5 mg/kg q6h.	(NA)
Penicillin Agents (time-dependent)								
Amoxicillin	365.4	0.75	20	0.26-0.31	1	5-20	500 mg q8h	NA
Ampicillin/ (Sulbactam 2:1)	349.4	0.88	20	0.38	1-1.9	15-20	3g q8h	CVVH 3g q12h CVVHD or CVVHDF 3g q8h
Azlocillin	461.5	0.2	30-46	0.21	1.3-1.5	5-6	3.0 g q4h/4.0 g q6h	3g q24h

Antimicrobial Agent	**MW**	**LogP**	**PPB**	**V_d [L/Kg]**	**$T_{1/2}$ (h)**	**T1/2anuria (h)**	**Standard Dosage**	**Dosage Adjustment on CRRT**
Flucloxacillin	453.9	2.69	95	0.14	0.75-1.5	2.3-2.8	2.0 g q4-6h	2g q6h or 1g q4h

Mezlocillin	539.6	0.21	16-42	0.14-0.24	0.7-1.1	6	3.0 g q6h	2g q24h
Nafcillin	414.5	3.21	90	0.24	0.5-1	4	2.0 g q4h	2g q4-6h
Oxacillin	401.4	2.05	92-96	0.2	0.5	1	4.0 g q4-6h	2g q4-6h
Penicillin G	334.4	1.92	65	0.2-0.7	0.5-1	5	0.8-4.0 millionU q4-6h	2 million U q12h
Piperacillin/ (Tazobactam 8:1)	517.6	0.65	16	0.18-0.3	1	5-6	4.5 g q6h	4,0g/0.5g q6-8h Depends on partial CLR preserved and in setting at high risk of pathogens with borderline susceptibility (MIC 32-64 mg/ml)
Ticarcillin/ (Clavulanate 30:1)	384.4	0.99	45-65	0.21	1.1	13	3.1 g q6h	CVVH 2g q6-8h CVVHD or CVVHDF 3.1 g q6h
Oxazolidinone Agents (time-dependent)								
Linezolid	337.3	0.61	31	0.64	4.7	5.4	600 mg q12h	600 mg q12h HV-HF 600mg q8 h the non –CRRT related clearance represents the most factor in interpatient variability
Tedizolid	450.3	0.82	70-90	1-1.14	11	11	200 mg q24h	In vitro study
Tetracycline Agents (time-dependent, concentration-enhanced, with PAE)								

Doxycycline	444.4	-0.72	80-93	0.75	15-24	18-25	100-200 mg q24h	100mg q24h
Tigecycline	585.6	0.66	71-89	7-9	42	42	50 mg q12h	50-100mg q12h
Antifungal Agents								
Azole								
Fluconazole	306.3	0.58	12	0.7	27	100	400-800 mg q24h	0.8 g q24h CVVH with Q_{UF} up to 2L/h or 0.4-0.6 g q 12h CVVHDF
Itraconazole, IV	705.6	5.48	99.8	10	21	35	200 mg q12h or q24h	100-200mg q 12h
Posaconazole	700.8	4.71	98.2	5-25	35	35	200-400 mg q12h	NA
Voriconazole, IV	349.3	1.65	58	4.6	12	13.7	6 mg/kg q12h twice, then 4 mg/kg q12h	6 mg/kg q12h twice, then 4 mg/kg q12h*
Antimetabolite								
Flucytosine	129.1	-0.24	4	0.6-0.9	4	85	25-37.5 mg/kg q6h	25-37.5 mg/kg q6h
Echinocandine								
Caspofungin	1093.3	0.17	97	9.67	9-11	13	70 mg once, then 50 mg q24h	70 mg once, then 50 mg q24h

Anidulafungina	1140.2	1.87	>99	0.6	40-50	40-50	LD 200mg first day MD 100mg q24h	CVVHDF LD 200mg first day MD 100mg q24h
Micafungin	1270.3	0.67	>99	0.39	10-15	10-15	100-150 mg q24h	
Polyene								
Amphotericin B **Lipid formulations (lipix complex AMPB-LC or liposomial L- AMPB)**	924.1	-0.66	>90	4	173	173	5 mg/kg q24h	3-5 mg/kg q24h
Antituberculous Agents								
Ethambutol	204.3	-0.12	20-30	1.6-3.89	2.5-4	7-15	15-25 mg/kg q24h	15-25 mg/kg q24h
Isoniazid	137.1	-0.71	15	0.57-0.76	0.7-4	8-17	300 mg q24h	300 mg q24h
Rifampicin	822.9	3.85	89	0.93	3.5	11	600 mg q24h	600 mg q24h

logP predicted values were calculated by ALOGPS

*Itraconazole and voriconazole are available in oral and parenteral formulations. The parenteral formulations are solubilized in a cyclodextrin diluent, which is eliminated by the kidneys and will accumulate in patients with renal insufficiency. The clinical significance of cyclodextrin accumulation in humans is not fully understood[5].