Principles of Antibacterial Dosing in Continuous Renal Replacement Therapy

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Key Words

Acute renal failure • Antibacterial agents • Continuous renal replacement therapy • Pharmacodynamics • Pharmacokinetics

Abstract

Background: Appropriate antibacterial therapy is important to maximize patient survival in sepsis. Acute renal failure complicates optimal antibiotic administration. **Methods:** MEDLINE search from 1986 to 2010 using the terms 'acute renal failure', 'pharmacokinetics', 'clearance', 'dosage', 'h(a)emofiltration', 'h(a)emodialysis', 'h(a)emodiafiltration', 'continuous renal replacement therapy', 'antibiotics', 'intensive care' and 'critically ill'. **Results:** Maximal bacterial killing and minimization of side effects depend on achieving pharmacokinetic targets appropriate to the selected antibacterial agent. Volume of distribution and clearance may be altered by critical illness and/or acute kidney injury. Clearance is determined by nonrenal clearance, residual renal clearance and continuous renal replacement therapy dose. Sieving and saturation coefficients are membrane specific, but may be altered by changes in protein binding induced by critical illness. A significant proportion of studies failed to report the essential dataset required for adequate antibacterial dosage calculation. **Conclusions:** Individualized dosing

based on first principles may be the most appropriate method of dosing, particularly when enhanced by therapeutic drug monitoring.

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Sepsis is the single most common cause for acute kidney injury (AKI) in the critically ill [1, 2]. Despite limited prospective data, there is evidence to indicate that these patients have greater physiological disturbance, more severe organ dysfunction and higher mortality compared to those with nonseptic AKI [2, 3]. As a result, optimal dosing of antibacterials in relation to the in vitro minimum inhibitory concentration (MIC) may be even more important to maximize bacterial killing while minimizing toxicity [4]. Unlike many other drugs, where the dose can be individually titrated to be effective, the optimal dose of antibacterials is currently based on theoretical considerations and data are largely derived from noncritically ill patients. To appropriately dose critically ill patients with AKI a thorough understanding of the relevant issues is required.

The major issues related to dosing of antibacterials in critically ill patients with AKI are that antibacterial pharmacokinetics may be altered by both acute renal failure and critical illness and are affected by renal replacement

Table 1. Equations for calculating CRRT clearance from the first principles

Mode of CRRT	Calculation of CRRT clearance
CVVH (postdilution)	$Cl_{CVVH}(\text{post}) = Q_f \times S_c$
CVVH (predilution)	$Cl_{CVVH}(\text{pre}) = Q_f \times S_c \times Q_b / (Q_b + Q_{\text{rep}})$
CVVHD	$Cl_{CVVHD} = Q_d \times S_d$
CVVHDF	$Cl_{CVVHDF} = (Q_f + Q_d) \times S_d$

$Cl_{CVVH}(\text{post})$ = Clearance from CVVH using post-filter hemodilution; Q_f = ultrafiltrate rate; $Cl_{CVVH}(\text{pre})$ = clearance from CVVH using pre-filter hemodilution; Q_b = blood flow rate; Q_{rep} = predilution replacement rate; Cl_{CVVHD} = clearance from CVVHD; Cl_{CVVHDF} = clearance from CVVHDF; Q_d = dialysate flow rate.

therapy. Renal replacement therapy in the critically ill is not a homogeneous entity, instead there is considerable variation in mode and dose and a discrepancy between prescribed and actual dose and the relationship between pharmacokinetics and pharmacodynamics of individual antibacterials needs to be taken into account. We will review the relevant literature and propose a systematic approach to antibacterial dosing that takes these factors into account.

Pharmacokinetic Factors

Following administration of a drug, the initial fall in concentration is due to the distribution of the drug through the various body compartments. The extent of this distribution is reflected by the volume of distribution (Vd). Thereafter falls in concentration are predominantly dependent on clearance.

Sepsis is a complex process which is commonly initiated by endotoxins. It is characterized by the activation of multiple endogenous mediators, such as cytokines, interleukins, platelet-activating factor, eicosanoids, complement components and kinins [5, 6]. Vascular endothelial dysfunction occurs either directly or indirectly, resulting in an increased capillary permeability. In conjunction with the maldistribution of blood flow, capillary leak syndrome ensues [7, 8]. Leakage of fluid from the intravascular compartment to the interstitial space would be expected to increase Vd and reduce serum concentration of hydrophilic drugs such as β -lactams and aminoglycosides [9, 10]. However, experimental data suggest the situation is more complex. For example, the Vd of ceftriaxone appears to be increased by critical illness and sep-

sis [11]; however, the Vd of meropenem is not [12–18]. Amikacin Vd is higher in critically ill septic patients than in healthy volunteers [19].

AKI may also affect antibacterial pharmacokinetics. In addition to a reduction in renal clearance, it may result in changes in Vd. For example, ceftriaxone [11], ceftazidime [20, 21] and netilmicin [19] Vd are increased in patients with acute renal failure.

Disease states which are common amongst the critically ill, such as uremia, cirrhosis, nephrotic syndrome, epilepsy, hepatitis and severe burns, have been shown to decrease protein binding of drugs. In addition, systemic pH, heparin, free fatty acids, and drugs such as salicylate and sulfonamide may act as competitive displacers for drug binding [22].

While Vd determines the initial or loading dose, subsequent doses are determined by total drug clearance. In patients with acute renal failure, total clearance is the sum of continuous renal replacement therapy (CRRT) and non-CRRT clearance (mainly residual renal and hepatic clearance).

CRRT is now typically performed via the venovenous route either as continuous venovenous hemofiltration (CVVH), hemodialysis or a combination of the two – hemodiafiltration (CVVHDF). In CVVH, the predominant mechanism of solute removal is by means of convective clearance where hydrostatic pressure gradient is generated across a filter membrane. Replacement fluid can be added to the circuit either before blood reaches the membrane (predilution) or after passage over the filter membrane (postdilution). For CVVH operating in postdilution mode, a correction factor (CF) needs to be used to calculate clearance ($CF = Q_b / (Q_b + Q_{\text{rep}})$) where Q_b and Q_{rep} represent blood flow rate and replacement rate, respectively.

In contrast, the predominant mechanism of solute removal in continuous venovenous hemodialysis is by means of diffusive clearance. This is achieved by generating a continuous concentration gradient using a counter-current flow of plasma and dialysate fluid, between which equilibration occurs. In CVVHDF, the two mechanisms of convective and diffusive clearance are combined to provide solute removal. The major factors determining clearance by each mode of CRRT are given in table 1.

The concentration of drug in ultrafiltrate or dialysate relative to plasma is expressed as sieving coefficient (S_c) or saturation coefficient (S_d), respectively. Passage of antibacterials across the filter membrane is essentially independent of drug molecular weight as the pore size of modern membranes vastly exceeds the size of most com-

monly used antibacterials. As a result, drug protein binding is the major determinant of both S_c and S_d . In general, S_c ranges from 0 to 1. It has been suggested that S_c can be estimated from published values of protein binding (PB), such that $S_c = 1 - PB$. Measured S_c and S_c estimated from published values of protein binding are correlated [23]. However, as discussed below, protein binding in the critically ill is variable and for some drugs (e.g. levofloxacin) S_c varies widely [24–28]. Furthermore, S_c may be affected by membrane material, drug-membrane interactions and flux properties. Similar to S_c , the value of S_d for any given drug may be membrane specific and subject to drug-membrane interactions. An increase in unbound drug will increase S_c and S_d and hence elimination by CRRT. For example, the unbound fraction of ceftriaxone is increased in patients with critical illness and is further increased by renal failure [11]. As a result, clearance of ceftriaxone by CRRT is likely to be higher than would be expected from protein binding in healthy volunteers, and this is confirmed by experimental data [29, 30]. Furthermore, S_d may be affected by blood and dialysate flow. At high blood flow the transit time may be insufficient for complete equilibration across the membrane, particularly for filters with a small surface area, resulting in a decrease in S_d [31]. Similarly, an increase in dialysate flow rate will reduce drug concentration in the dialysate and hence decrease S_d . Nevertheless, at the blood (150–200 ml/min) and dialysate flow rates (<35 ml/min) typically used during CRRT, clearance is linearly related to dialysate flow rate indicating that S_d is constant under these conditions [32].

In general, drugs with a large V_d are poorly eliminated by CRRT as the plasma concentration of drug is low relative to the amount of drug in the body. This has led to the recommendation that supplemental dosing of these drugs is unnecessary [33]. However, for the lipophilic fluoroquinolones, such as ciprofloxacin and levofloxacin, V_d s are large (>1.5 liters/kg) but renal clearance still accounts for $\geq 70\%$ of total clearance [34, 35]. The elimination half-life of both drugs approaches that of normal healthy volunteers with increasing ultrafiltration and/or dialysate flow rate necessitating higher daily doses than previously recommended [25]. If, however, the reason for increased V_d is a fall in protein binding, elimination by CRRT (and kidneys) will be affected by an increase in the free fraction of the drug. In general, drugs with a high V_d (>1 liter/kg) and high protein binding (>80%) are poorly eliminated by CRRT [36].

The Gibbs-Donnan effect refers to the effect of retained anionic protein (such as albumin) on the blood side of the

filter membrane. This could lead to transient retention of cationic drugs such as aminoglycosides and levofloxacin. Anionic drugs such as ceftazidime and cefotaxime may be repelled [22]. However, the clinical relevance of this effect is unclear [23, 37, 38]. Adsorption of antibacterials to the filter may also result in drug elimination. Limited in vitro data suggest that adsorption is both membrane and drug dependent [37–39]. At clinically relevant concentrations, adsorption of levofloxacin and vancomycin is unlikely to be clinically significant [37, 39]; however, a significant amount of amikacin binds irreversibly to sulfonated polyacrylonitrile membranes in vitro [38]. The clinical importance of adsorption of antibacterials is currently unknown but warrants further investigation.

Non-CRRT clearance is predominantly determined by residual renal function and hepatic clearance. However, alternative elimination pathways such as transintestinal excretion (e.g. for ciprofloxacin) may represent compensatory mechanisms that prevent accumulation in patients with renal failure [40]. Renal elimination is to a large extent determined by glomerular filtration rate, with contributions from tubular secretion and reabsorption, but the ability to upregulate clearance is relatively limited. Hepatic clearance, however, may be variable depending on the degree of underlying organ failure. Hepatic dysfunction not only occurs in those with acute liver failure or decompensated chronic liver disease, but it is also a common entity in the critically ill [41, 42]. In contrast, for those without concomitant hepatic dysfunction, hepatic drug clearance may actually increase in the presence of acute renal failure [43, 44]. Quantitative or at least qualitative evaluation of hepatic function should therefore be considered prior to formulating an antibacterial dosing regime, in particular for agents with multiple routes of clearance (i.e. ciprofloxacin and meropenem).

The relationship between pharmacokinetic endpoints and pharmacodynamic outcomes varies between classes of antibacterials. Understanding of these relationships is important in determining dosing regimes in order to maximize efficacy, minimize the development of resistance and minimize the risk of toxicity [10]. Broadly, antibacterials fall into three groups: those with time-dependent killing, those with concentration-dependent killing and those with both time- and concentration-dependent killing. These kill characteristics have been previously determined under in vitro conditions. For each group, there is a pharmacokinetic target that is most closely associated with optimal killing. These targets are often quoted in reference to the MIC (table 2) and can be used to guide dosing regimes [45].

Table 2. Kill characteristics of different antibacterials and pharmacokinetic targets associated with optimal bacterial killing

Antibacterials	Killing characteristics	Pharmacokinetic targets
β -Lactams	time dependent	40–100% of dosing interval >MIC or 40–100% of dosing interval >5 times MIC [47]
Aminoglycosides	concentration dependent	$C_{\max}$:MIC 8–10 [53]
Fluoroquinolones	concentration dependent/ time dependent	$C_{\max}$:MIC 6–8, AUC_{24} :MIC 100–125 (Gram-negatives), 34 (<i>S. pneumoniae</i>) [87, 91]
Vancomycin	concentration dependent	AUC_{24} :MIC ≥ 400 (vs. <i>Staphylococcus aureus</i>) [77]
Linezolid	concentration dependent	AUC_{24} :MIC 50 (<i>S. pneumoniae</i>), AUC_{24} :MIC 82 (<i>S. aureus</i>) [92]
Macrolides, azalides, ketolides	concentration dependent	probably AUC_{24} :MIC (drug concentration at target site). Relevance of plasma concentrations doubtful given the fact that drugs are concentrated in tissue [90]
Metronidazole	concentration dependent	not established

The β -lactams, comprising penicillins, cephalosporins, carbapenems and monobactams, are the classic example of antimicrobials which exhibit time-dependent killing. They have a slow continuous bactericidal effect and killing is most closely related to the duration of time for which the serum concentration exceeds a threshold concentration. Further increases in concentration above the threshold do not increase killing. The appropriate threshold is not clearly established but varies between 1 and 5 times MIC [46]. The duration of time for which the serum concentration should exceed the threshold is also unclear with recommendations ranging from 40 to 100% of the dosing interval [47] depending on the target organism and the choice of β -lactams. The optimal duration is, in part, related to the postantibiotic effect of β -lactams. Postantibiotic effect refers to the continued suppression of bacterial growth even when drug concentrations fall below the MIC of the bacteria [48]. β -Lactams have a significant postantibiotic effect against Gram-positive organisms but, with the exception of carbapenems, not Gram-negatives. As a result, it has been proposed that, in the absence of any postantibiotic effect, the serum concentration of β -lactam antibacterial agent should exceed the MIC for the respective organism for 90–100% of the dosing interval [49]. However, for carbapenems, 40% may be sufficient [50]. Furthermore, resistant strains are likely to emerge when the antibacterial level falls below the MIC for more than half of the dosing interval [51].

Aminoglycosides are the classic example of concentration-dependent killing. Bactericidal activity is associated with the postdistribution peak plasma concentration ($C_{\max}$) to MIC ratio ($C_{\max}$ /MIC) both in vitro [52] and in

vivo [53]. An optimal $C_{\max}$ /MIC ratio of 8–10 has been recommended [48, 53–55], and this is best achieved by the extended interval dosing regime where larger doses are given less frequently. In patients with normal renal function, doses are often given once daily. Aminoglycosides demonstrate a significant postantibiotic effect (>3 h), the duration of which is concentration dependent [53, 56–61] and, therefore, the postantibiotic effect is enhanced by the administration of larger doses at extended time intervals. Furthermore, an extended interval dosing regime should result in lower trough concentrations and therefore reduce toxicity. This has been confirmed in clinical studies which have demonstrated a comparable, if not superior outcome with less toxicity compared to conventional multiple dosing regimes [62–65].

The fluoroquinolones (ciprofloxacin, levofloxacin and moxifloxacin) typically exhibit combined concentration- and time-dependent kill characteristics. Previous research has suggested that achieving a $C_{\max}$ /MIC ratio of 10 for fluoroquinolones is the critical variable in predicting bacterial eradication [66]. Others have proposed that dosing should maximize the ratio of area under the concentration time curve (AUC) to MIC in 24 h (AUC_{24} /MIC) [67]. An AUC_{24} /MIC ratio of >125 and >30 has been recommended for Gram-negative and Gram-positive organisms, respectively [4]. Others have also shown that a high AUC_{24} /MIC can reduce the development of resistance [68–70] and for Gram-negative organisms and that resistance may occur when the AUC_{24} /MIC is <100 [23, 71]. Therefore, it is important that threshold AUC_{24} /MIC ratios need to be obtained for the optimal dosing of fluoroquinolones.

Avoidance of toxicity is an important consideration when designing dose regimens. However, while toxicity is associated with drug concentrations, the relationship is not simple and is dependent on a large number of factors, which may vary from agent to agent [72–76]. High trough concentrations appear to be associated with aminoglycoside toxicity. Vancomycin toxicity has similarly been linked to trough concentrations; however, these data are based on only 8 patients with evidence of nephrotoxicity [77]. β -Lactam neurotoxicity is most closely associated with renal failure. This is in part due to decreased clearance but also increased CNS penetration as a result of altered protein binding and increased permeability of the blood-brain barrier [76, 78]. As a result, the relationship between blood concentration and toxicity may be complex. For example, cefepime neurotoxicity has been associated with a wide range of blood concentrations [79] and has even been reported in a patient with normal renal function and receiving a usual dose of cefepime [80]. Furthermore, there are no data relating specific serum pharmacokinetic endpoints with β -lactam toxicity. In rats, fluoroquinolone-induced seizures are associated with high peak plasma concentrations [81] and this militates against an extended-interval dosing strategy for fluoroquinolones aimed at maximizing $C_{\max}/\text{MIC}$ ratio instead of $\text{AUC}_{24}/\text{MIC}$ ratio.

Critique of Currently Available Dosage Regimes

Dosage recommendations for patients with renal dysfunction are available in most drug inserts, textbooks and antibiotic guidelines. Pharmacokinetic data are either derived from healthy individuals or those with chronic renal failure with dosage adjustment based on creatinine clearance. Estimated glomerular filtration rate may be used as a surrogate for creatinine clearance and the average daily effluent rate can be substituted for the glomerular filtration rate. However, it is important to note that recommendations for patients with chronic renal failure undergoing intermittent renal replacement therapy are not appropriate for the critically ill because of differences in the mode of renal replacement therapy as well as pharmacokinetic differences [82]. Other recommendations use a fixed and suboptimal effluent rate [83] or do not take the dose of CRRT into account [33].

An alternative approach is to use doses recommended in studies of the pharmacokinetics of antibacterials in critically ill patients receiving CRRT. However, dosages based on the findings of individual studies may not be

appropriate unless the mode and dose of CRRT being used are similar to those in the study. The mode and dose of CRRT are highly variable, not only between studies but also within studies (table 3). In a recent review of the literature, 12% of studies reviewed omitted even basic information such as ultrafiltrate/dialysate rate and 14% made no dose recommendation. Furthermore, in only 8% was the dose recommendation referenced to a pharmacokinetic target based on MIC [84].

There is also a number of dose adjustment equations proposed for critically ill patients requiring CRRT (table 4). These equations either assume that measurement of antibacterial concentrations is widely available or that S_c can be accurately estimated from data on protein binding obtained from the noncritically ill or are based on either downward adjustment from those with normal renal function or upward adjustment from those with chronic renal failure with anuria. However, 'normal' doses or doses recommended for anuric patients may not achieve pharmacokinetic targets associated with improved outcome. For example, based on pharmacokinetic data in critically ill patients [85] and the MIC for *Streptococcus pneumoniae* [86], the recommended dose of moxifloxacin may not achieve an optimal $\text{AUC}:\text{MIC} > 33.7$ [87] in geographical localities in which the MIC is high but still below accepted breakpoints. Limitations of these formulae and their inherent flaws have been previously highlighted [88], with method 4 (table 4) consistently overestimating daily dosing needs for drugs with low nonrenal clearance and >3 -fold difference in the calculated dose of gentamicin and vancomycin between methods 3 and 4 (table 4).

From the above discussion, it can be seen that there are many factors that need to be taken into account when determining appropriate doses of antibacterial agents for critically ill patients receiving CRRT. None of the aforementioned dosing recommendations take all these factors into account. Given the variability in mode, dose of CRRT and the MICs in different ICUs, we believe the most appropriate way to dose antibacterials in patients receiving CRRT is to calculate an appropriate individualized dose from first principles (fig. 1).

As previously stated the initial dose is dependent on the V_d and maintenance doses are dependent on total clearance (CRRT and non-CRRT clearance). Furthermore, antibacterial dosing needs to be adjusted according to the pharmacokinetic target associated with optimal killing. Thus appropriate dose calculation requires knowledge of the pharmacokinetic target (table 2) and the usual MIC of the suspected organism at the prescrib-

Table 3. Pharmacokinetic data for antibacterials commonly used in intensive care in patients receiving CRRT

Drug (ref. No.)	Mode of CRRT (number of patients)	Residual renal function	Vd	Non-CRRT clearance ¹	Membrane/ surface area
Penicillins					
Ampicillin (no data)					
Amoxicillin [93]	CVVH (12)	U/O <400 ml/12 h	NS	NS	CT/1.9 m ²
Piperacillin [94]	CVVH (6)	4 anuric patients 2 patients U/O <400 ml/24 h	0.48 ± 0.24 liter/kg	NS	PS/0.5 m ²
Piperacillin [94]	CVVH (4)	3 anuric patients 1 patient U/O = 220 ml/24 h	0.14 ± 0.07 liter/kg	NS	PS/0.5 m ²
Piperacillin [95]	CAVHD (12)	Cl _{urea} : 18.4 ± 2.3 ml/min	25.8 ± 3.8 liters	34.9 ± 21.2	AN69/0.43 m ²
Piperacillin-tazobactam [68]	CVVH (4)	Cl _{cr} : 8.67 ± 2.31 ml/min	piperacillin: 21.0 ± 11.7 liters, tazobactam: 18.9 ± 7.1 liters	piperacillin: 38.55 tazobactam: 29.5	AN69/0.9 m ²
Piperacillin-tazobactam [68]	CVVH (5)	Cl _{cr} : 25.20 ± 7.73 ml/min	piperacillin: 26.8 ± 19.8 liters, tazobactam: 21.6 ± 3.0 liters	piperacillin: 78.4 tazobactam: 46.3	AN69/0.9 m ²
Piperacillin-tazobactam [96]	CVVHD (8)	anuric	piperacillin: 0.31 ± 0.07 liter/kg, tazobactam: 0.24 ± 0.09 liter/kg	piperacillin: 49.5 ± 60.1 tazobactam: 23.7 ± 14.9	AN69/0.6 m ²
Ticarcillin-clavulanate [97]	CVVH (3)	2 patients anuric 1 patient U/O >2 liters/day	ticarcillin: 0.26 liter/kg (n = 2, with ECMO), 0.25 liter/kg (n = 1, without ECMO) clavulanate: 0.86 liter/kg (n = 2, with ECMO), 0.33 liter/kg (n = 1, without ECMO)	ticarcillin: 5.75 (n = 2, with ECMO), 40.83 (n = 1, without ECMO) clavulanate: 61.75 (n = 2, with ECMO), 186.8 (n = 1, without ECMO)	PS/0.25 m ²
Flucloxacillin [93]	CVVH (5)	U/O <400 ml/12 h	NS	NS	CT/1.9 m ²
Flucloxacillin [98]	CVVH (10)	anuric	0.54 ± 0.43 liter/kg	106.9	PA/0.7 m ²
Oxacillin (no data)					
Nafcillin (no data)					
Cloxacillin (no data)					
Cephalosporins					
Cefuroxime [99]	CAVHD (12)	NS	22.8 ± 9.2 liters	1.5	AN69/0.43 m ²
Cefuroxime [100]	CAVH (3)	Cl _{cr} <1 ml/min	21 ± 2.5 liters	21 ± 6.6	PS/0.6 m ²
Cefotaxime (no data)					
Ceftazidime [99]	CAVHD (9)	NS	31.1 ± 14.6 liters (5)	15.15	AN69/0.43 m ²
Ceftazidime [101]	CVVH (12)	anuric	0.41 ± 0.16 liter/kg	66.57 ± 12.90	PS/0.7 m ²
Ceftazidime [102]	CVVH/CVVHD (8)	Cl _{cr} <20 ml/min	NS	NS	AN69/0.6 m ² PMMA/2.1 m ² PS/0.65 m ²
Ceftazidime [103]	CVVHDF (7)	Cl _{cr} ≤5 ml/min	0.25 ± 0.09 liter/kg	28.9 ± 5.6	AN69/0.6 m ²
Ceftazidime [21]	CVVHDF (2)	Cl _{cr} = 0 ml/min	0.46 liter/kg	24.95	AN69/0.9 m ²
Ceftazidime [93]	CVVH (7)	U/O <400 ml/12 h	NS	NS	CT/1.9 m ²
Ceftriaxone [104]	CVVH (6)	Cl _{cr} <10 ml/min	0.42 ± 0.21 liter/kg	22.7 ± 19.1	PA/1.4 m ²
Ceftriaxone [105]	CVVH (5)	ESRD	NS	NS	AN69/0.6 m ²
Ceftriaxone [105]	CVVH (5)	ESRD	NS	NS	PMMA/2.1 m ²
Ceftriaxone [105]	CVVH (5)	ESRD	NS	NS	PS/0.65 m ²
Cefepime [93]	CVVH (2)	Cl _{cr} = 29 ml/min (1)	0.65 liter/kg	NI	AN69/0.9 m ²
Cefepime [106]	CVVHDF (2)	Cl _{cr} <10 ml/min Cl _{cr} = 35 ml/min	0.6 liter/kg	NI	AN69/0.9 m ² PS/1.4 m ²
Cefepime [107]	CVVH (5)	U/O <155 ml/24 h	0.46 ± 0.14 liter/kg	23	AN69/0.6 m ²
Cefepime [107]	CVVHDF (7)	U/O <67 ml/24 h	0.34 ± 0.1 liter/kg	21	AN69/0.6 m ²
Cefoperazone (no data)					
Monolactams					
Aztreonam (no data)					
Carbapenems					
Imipenem [108]	CVVH (6)	2 anuric patients 4 patients U/O <43 ml/24 h	0.36 ± 0.10 liter/kg	109 ± 24	AN69/0.6 m ²
Imipenem [108]	CVVHDF (6)	2 anuric patients 4 patients U/O <135 ml/24 h	0.37 ± 0.13 liter/kg	120 ± 32	AN69/0.6 m ²
Imipenem-cilastatin [109]	CAVH (6)	2 anuric patients 4 patients U/O <350 ml/24 h	imipenem: 0.29 ± 0.03 liter/kg cilastatin: 0.27 ± 0.07 liter/kg	imipenem: 108.5 ± 29.6 cilastatin: 20.6 ± 30.3	PS/NS
Imipenem-cilastatin [110]	CVVH (12)	10 anuric patients 2 patients U/O = 200 ml/8 h	imipenem: 24.3 ± 7.7 liters cilastatin: 19.6 ± 7.3 liters	imipenem: 90.8 ± 26.3 cilastatin: 13.2 ± 13.9	AN69/NS

S _c		S _d	Dose recommended by authors	Total effluent rate (range, unless otherwise specified)	Remarks
pre	post				
0.71 ± 0.16; route of dilution	NS	NA	NS	mean ± SD: 29 ± 7 ml/kg/h	first-dose pharmacokinetics
NS	NS	NS	4 g 12 hourly	0.76 ± 0.20 to 0.88 ± 0.18 liters/h	
NS	NS	NS	4 g 12 hourly	0.50 ± 0.08 to 0.72 ± 0.14 liters/h	
NA	NA	0.71 ± 0.21	150% of dose for anuric patients	mean ± SD: 1.22 ± 0.09 liters/h	
piperacillin: 0.42 ± 0.25 tazobactam: 0.76 ± 0.26	NA	NA	NS	mean ± SD: 1.63 ± 0.47 liters/h	children (2 patients receiving concomitant ECMO, 1 patient without ECMO U/O >2 liters/day)
piperacillin: 0.38 ± 0.37 tazobactam: 0.73 ± 0.32	NA	NA	NS	mean ± SD: 1.82 ± 0.26 liters/h	
NA	NA	piperacillin: 0.87 ± 0.21 tazobactam: 0.64 ± 0.19	NS	1.58–1.70 liters/h	
ticarcillin: 0.72 (n = 2, with ECMO), 1.06 (n = 1, without ECMO) clavulanate: 1.81 (n = 2, with ECOM), 1.44 (n = 1, without ECMO); route of dilution NS	NS		NS	0.82–0.95 liter/h	
0.33 ± 0.34 (0.2 in 4 patients and 0.94 in 1 patient); route of dilution	NS	NA	NS	mean ± SD: 23 ± 7 ml/kg/h	
NA	0.21 ± 0.09	NA	4 g 8 hourly	mean ± SD: 3.42 ± 0.54 liters/h	
NA	NA	0.90 ± 0.33	500–750 mg 12 hourly	1–2 liters/h	not critically ill
NA	NA	NA	initial 1.5 g, then 750 mg 20–24 hourly	mean ± SD: 0.85 ± 0.11 liter/h	
NA	NA	0.86 ± 0.08	500 mg 12 hourly	1–2 liters/h	ceftriaxone not recommended for patients given calcium-containing i.v. solutions
NA	0.69 ± 0.18	NA	2 g 8 hourly (MIC <4 mg/l); 3 g 8 hourly (MIC = 8 mg/l)	mean ± SD: 2.82 ± 0.42 liters/h	
AN69: 0.97 ± 0.11, PMMA: 0.80 ± 0.19, polysulfone: 0.97 ± 0.13 (no replacement fluid given)		NS	initial 1 g, then 250–500 mg 12 hourly	CVVH 0.5–1 liter/h CVVHD 0.5–2 liters/h	
NA	NA	0.81 ± 0.11	initial 2 g, then 3 g daily by continuous infusion	2.5 liters/h	predilution
NA	NA	0.9	NS	1.5–2 liters/h	predilution
0.87 ± 0.46; route of dilution NS	NA	NS	mean ± SD 25 ± 7 ml/kg/h		
NA	0.69 ± 0.39	NA	2 g daily	1.2–1.8 liters/h	
0.48 ± 0.13; no replacement fluid administered		NA	NS	0.5–1 liter/h	
0.86 ± 0.33; no replacement fluid administered		NA	NS	0.5–1 liter/h	
0.82 ± 0.22; no replacement fluid administered		NA	NS	0.5–1 liter/h	
0.62	NA	NA	2 g 8 hourly	1.0–2.1 liters/h	predilution
NA	NA	AN69 0.83, PS 0.97	2 g 8 hourly	2.14–2.5 liters/h	
NA	0.86 ± 0.04	NA	2–4 g daily	0.54–1.14 liters/h	
NA	NA	0.78 ± 0.10	2–4 g daily	1.78–2.35 liters/h	
NA	1.21 ± 0.11	NA	1–1.5 g/day (MIC ≤2 mg/l); ≥2 g/day (MIC 4–8 mg/l)	0.78–1.44 liters/h	
NA	NA	1.28 ± 0.17	1–1.5 g/day (MIC ≤2 mg/l); ≥2 g/day (MIC 4–8 mg/l)	2.0–2.4 liters/h	
1.16/0.7; route of dilution	NS	NA	NS	0.24–7.9 liters/h	
imipenem: 1.2 ± 0.1 cilastatin: 0.8 ± 0.2; route of dilution	NS	NA	0.5 g daily	1.1–1.2 liters/h	

Table 3 (continued)

Drug (ref. No.)	Mode of CRRT (number of patients)	Residual renal function	Vd	Non-CRRT clearance ¹	Membrane/surface area
Imipenem-cilastatin [111]	CVVHD (6)	anuric	imipenem: 0.37 ± 0.16 liter/kg cilastatin: 0.26 ± 0.09 liter/kg	imipenem: 70.6 ± 18.1 cilastatin: 18.0 ± 9.9	PAN/0.5 m ²
Imipenem-cilastatin [112]	CAVH or CAVHDF (8)	NS	NS	NS	AN69/0.6 m ²
Imipenem [113]	CVVH (7)	NS	0.33 ± 0.09 liter/kg	NI	PS/0.25 m ²
Meropenem [13]	CVVH (9)	anuric	0.36 ± 0.07 liter/kg	94.0 ± 26.9	PS/0.43 m ²
Meropenem [14]	CVVHDF (9)	anuric	0.26 ± 0.09 liter/kg	22.7	AN69/0.9 m ²
Meropenem [114]	CVVH (9)	Cl _{cr} = 1.3 ml/min	12.4 ± 1.8 liters	29.9 ± 5.4	AN69/NS
Meropenem [15]	CVVH (5)	NS	0.38 ± 0.12 liter/kg	NI	AN69/0.9 m ²
Meropenem [15]	CVVHDF (5)	NS	0.31 ± 0.08 liter/kg	NI	AN69/0.9 m ²
Meropenem [16]	CVVH (8)	U/O <500 ml/24 h	0.28 ± 0.07 liter/kg	58.52 ± 24.46	AN69/0.9 m ²
Meropenem [115]	CVVHDF (7)	Cl _{cr} = 1.14 ml/min	0.57 ± 0.29 liter/kg	123.26	AN69/1.4 m ² PS/0.9 m ²
Meropenem [115]	CVVH (4)	Cl _{cr} = 12.5 ± 12.1 ml/min	0.38 ± 0.07 liter/kg	114.38 ± 51.78	AN69/1.4 m ² PS/0.9 m ²
Meropenem [115]	CVVHDF (3)	Cl _{cr} = 24.8 ± 18.1 ml/min	0.36 ± 0.14 liter/kg	85.92 ± 75.83	AN69/1.4 m ² PS/0.9 m ²
Meropenem [116]	CVVHDF (6)	NS	median (IQR) 32.3 liters (28.9–40.7)	NS	PS/1.4 m ²
Meropenem [116]	CVVHDF (6)	NS	NS	NS	PS/1.4 m ²
Meropenem [18]	CVVH (5)	1 patient anuric 4 patients U/O <50 ml/24 h	0.37 ± 0.15 liter/kg	59 ± 17.7	PAN/0.6 m ²
Meropenem [117]	CVVHDF (12)	10 patients anuric 2 patients U/O <180 ml/24 h	0.49 ± 0.16 liter/kg	46.96 ± 29.61	AN69/0.9 m ²
Meropenem [118]	CVVH (10)	oliguric or anuric	median (IQR) 0.37 liter/kg (0.32–0.46)	median (IQR) 40 (26.7–50.0)	AN69/2.15 m ²
Doripenem [119]	CVVHDF (6)	Cl _{cr} 9.0 ± 4.1 ml/min	0.59 ± 0.33 liter/kg	44.5	PS/1.0 m ²
Biapenem [120]	CVVHDF (9)	NS	0.50 ± 0.23 liter/kg	150.8 ± 67.5	PMMA/NS
Biapenem [121]	CVVHDF (7)	NS	10.8 ± 2.9 liters (central compartment)	102.3 ± 31.5	PMMA/NS
Ertapenem (no data)					
Quinolones					
Moxifloxacin [122]	CVVHDF (9)	anuric	270 ± 133 liters	291	AN69/0.9 m ²
Levofloxacin [27]	CVVH (12)	anuric	4.3 ± 1.8 liters/kg	NS	PA/0.7 m ²
Levofloxacin [26]	CVVH (4)	1 patient anuric 3 patients U/O ≤40 ml/24 h	1.05 liter/kg	30.8	AN69/0.6 m ²
Levofloxacin [26]	CVVHDF (6)	U/O ≤128 ml/24 h	1.0 liters/kg	29.5	AN69/0.6 m ²
Levofloxacin [25]	CVVHDF (6)	Cl _{cr} <10 ml/min (6)	1.51 ± 0.52 liters/kg	28.0 ± 33.7	AN69/0.9 m ²
Levofloxacin [25]	CVVH (6)	Cl _{cr} <10 ml/min	1.42 ± 0.42 liters/kg	32.2 ± 27.5	AN69/0.9 m ²
Levofloxacin [28]	CVVH (4)	anuric	1.02 ± 0.66 liters/kg	26.3 ± 14.8	AN69/0.9 m ²
Ciprofloxacin [26]	CVVH (5)	1 patient anuric 4 patients U/O ≤155 ml/24 h	1.12 liters/kg	72	AN69/0.6 m ²
Ciprofloxacin [26]	CVVHDF (5)	2 patients anuric 3 patients U/O ≤90 ml/24 h	0.96 liter/kg	125.2	AN69/0.6 m ²
Ciprofloxacin [40]	CVVHDF (6)	NS	1.56 ± 0.35 liters/kg	NI	AN69/NS
Ciprofloxacin [93]	CVVH (16)	U/O <400 ml/12 h	NS	NS	CT/1.9 m ²
Ciprofloxacin [123]	CVVHDF (1)	NS	NS	NS	PA/0.6 m ²
Glycopeptides					
Vancomycin [93]	CVVH (6)	U/O <400 ml/12 h	NS	NS	CT/1.9 m ²
Vancomycin [124]	CVVH (5)	end-stage renal failure	NA	NS	AN69/0.6 m ² PMMA/2.1 m ² PS/0.65 m ²
Vancomycin [125]	CVVHDF (10)	NS	49.7 ± 29.1 liters	NI	AN69/NS
Vancomycin [126]	CVVH (10)	anuric	0.55 ± 0.12 liter/kg	16.2 ± 7.0 (range 3.8–23.3)	PS/0.25 m ²
Vancomycin [127]	CVVH (2)	U/O ≤46 ml/24 h	41.7 liters, 55.8 liters	10	PAN/0.6 m ²
Vancomycin [128]	CVVH (7)	NS	NS	NS	AN69/1.6 m ²
Teicoplanin [129]	CVVHDF (3)	Cl _{cr} = 2.41 ml/min	1.23 ± 0.77 liters/kg	7.84	NS
Teicoplanin [130]	CVVH (1)	Cl _{cr} = 35 ml/min	NS	NS	AN69/0.9 m ²
Teicoplanin [131]	CVVHDF (5)	Cl _{cr} 5.8 ± 2.7 ml/min	0.93 ± 0.42 liter/kg	NS	AN69/0.6 m ²
Teicoplanin [132]	CVVH (11)	U/O 545 ± 502 ml/24 h	0.84 ± 0.22 liter/kg	33.7 ml/kg/h	PS/1.2 m ²
Teicoplanin [132]	CVVH (4)	U/O 545 ± 502 ml/24 h	0.48 ± 0.09 liter/kg	5.0 ml/kg/h	PS/1.2 m ²

S _c		S _d	Dose recommended by authors	Total effluent rate (range, unless otherwise specified)	Remarks
pre	post				
NA	NA	NS	0.5 g each of imipenem and cilastatin 12 hourly	1.26–1.38 liters/h	
imipenem: 1.05 ± 0.19 cilastatin: 0.68 ± 0.08	NA	NS	0.5 g 12 hourly	1–3 liters/h	
route of dilution	NS	NA	0.5 g 6–8 hourly	1 liter/h	
NA	1.09 ± 0.10	NA	1 g 8 hourly	mean ± SD: 2.7 ± 0.4 liters/h	first-dose pharmacokinetics
NA	NA	NS	1 g 12 hourly	1.6–1.9 liters/h	
1.17 ± 0.11; route of dilution	NS	NA	1 g daily	1.1–1.15 liters/h	
NA	0.95 ± 0.03	NA	1 g 12 hourly	1.0–2.0 liters/h	
NA	NA	0.92 ± 0.08	1 g 12 hourly	2.0–3.0 liters/h	
0.91 ± 0.10		NA	500 mg 12 hourly	1.6 liters/h	
NA	NA	AN69 0.76 ± 0.15 PS 0.76 ± 0.08	NS	1.5–2.5 liters/h	predilution
AN69 0.80 ± 0.15, PS 1.01	NA	NA	NS	2.0–2.5 liters/h	
NA	NA	AN69 0.82 ± 0.14, PS 0.9	NS	2.0–2.8 liters/h	predilution
NA	NA	median (IQR) 0.97 (0.87–1.05)	initial 0.5 g, then 2 g over 24 h by continuous infusion	1.4–2.4 liters/h	first-dose pharmacokinetics
NA	NA	median (IQR) 0.89 (0.79–0.93)	initial 0.5 g, then 2 g over 24 h by continuous infusion	1.4–2.4 liters/h	
0.63 ± 0.25; route of dilution	NS	NA	0.5 g 12 hourly	1.5–1.8 liters/h	
NA	NA	0.65 ± 0.25	750 mg 8 hourly or 1.5 g 12 hourly	1.11–2.55 liters/h	predilution
0.93	NA	NA	1 g 8 hourly	median (IQR) 3.5 (3.4–3.9) liters/h	predilution
NA	NA	NS	250 mg 12 hourly	0.8 liter/h	postdilution
NA	NA	0.92 ± 0.10	300 mg 8 hourly	1.4 liters/h	postdilution
NA	NA	0.92 ± 0.06	300–600 mg 12 hourly	1.4 liters/h	postdilution
NA	NA	0.84 ± 0.16	400 mg daily	2 liters/h	predilution
0.47 ± 0.27; route of dilution	NS	NA	NS	mean ± SD: 3.2 ± 0.9 liters/h	
NA	0.62	NA	250 mg 24 hourly or 500 mg 48 hourly	0.8–1.3 liters/h	
NA	NA	0.61	250 mg 24 hourly 500 mg 48 hourly	2–2.4 liters/h	postdilution
NA	NA	0.73 ± 0.14	250 mg daily	mean: 2.2 liters/h	predilution
0.79 ± 0.14	NA	NA	200 mg daily	mean: 1.2 liters/h	
NA	0.98 ± 0.06	NA	initial 500 mg, then 250 mg daily	1.3 liters/h	
NA	NA	0.67	400 mg daily	0.54–1.26 liters/h	
NA	NA	0.63	400 mg daily	1.84–2.24 liters/h	
NA	NA	0.70 ± 0.13	300 mg 12 hourly	3 liters/h	predilution
0.89 ± 0.35; route of dilution	NS	NA	NS	mean ± SD: 27 ± 5 ml/kg/h	
NA	NA	mean ± SEM: 0.5 ± 0.067	NS	mean: 1.91 liters/h	
0.71 ± 0.19	NA	NA	NS	mean ± SD: 32 ± 9 ml/kg/h	
AN69: 0.70 ± 0.15 PMMA: 0.86 ± 0.16 PS: 0.68 ± 0.19		NA	initial 15–20 mg/kg, then 0.55–1.25 g daily (Cl _{cr} <20 ml/min)	0.5–1 liter/h	
NA	NA	0.70 ± 0.10	450 mg 12 hourly	3 liters/h	predilution
NS	NS	NA	NS	0.5–1.0 liter/h	
NA	0.88 ± 0.03 0.89 ± 0.03	NA	initial 15–20 mg/kg, followed after 24 h by 250–500 mg 12 hourly	1.5 liters/h	
0.76 ± 0.11	0.57 ± 0.15	NA	500 mg 6 hourly or 1 g 12 hourly	6 liters/h	high-volume CVVH
NA	NA	NS	NS	NS	
0.13–0.17	NA	NA	NS	1–2 liters/h	
NA	NA	NS	800 mg on day 1; 400 mg on days 2 and 3, then 400 mg 48–72 hourly	0.96 liter/h	
0.14 ± 0.03 (n = 2, predilution; n = 9, mixed dilution)		NA	1.2 g of loading dose, 0.6–1.8 g daily	35 ml/kg/h (2.4 ± 0.3 liters/h)	first-dose pharmacokinetics
0.17 ± 0.07	NA	NA	1.2 g of loading dose, 0.6–1.8 g daily	35 ml/kg/h (2.6 ± 0.1 liters/h)	

Table 3 (continued)

Drug (ref. No.)	Mode of CRRT (number of patients)	Residual renal function	Vd	Non-CRRT clearance ¹	Membrane/surface area
Aminoglycosides					
Gentamicin [133]	CAVH (4)	3 patients U/O <572 ml/24 h 1 patient U/O NS	0.36 ± 0.09 liter/kg	9.55 ± 9.82	PS/0.25 m ²
Gentamicin [134]	CAVHDF (5)	Cl _{cr} = 2.8 ml/min	NS	15.26 ± 7.09	PAN/0.43 m ²
Netilmicin [135]	CVVHDF (6)	Cl _{cr} = 22.3 ± 6.2 ml/min	24.92 ± 5.96 liters	NS	AN69/0.6 m ²
Amikacin [136]	CVVH (5)	anuric	35 ± 7.5 liters	22.6	PS/0.6 m ²
Amikacin [137]	CVVHDF (6)	NS	0.47 ± 0.08 liter/kg	NS	AN69/NS
Tobramycin [133]	CAVH (4)	2 patients anuric. 2 patients U/O 32 ml/24 h	0.28 ± 0.08 liter/kg	6.83 ± 3.22	PS/0.25 m ²
Arbekacin [138]	CVVHDF (3)	NS	7.76 liters (central compartment)	NS	PMMA/NS
Miscellaneous					
Colistin [139]	CVVHDF (1)	multiple organ failure	10.9 liters	37.5	AN69/NS
Linezolid [140]	CVVH (2)	U/O <200 ml/24 h	0.485 liter/kg	NS	AN69XT/ 1.65 m ²
Linezolid [141]	CVVH (2)	anuric	1.02 liters/kg	36.8	PS/1.25 m ²
Linezolid [142]	CVVH (7)	anuric	0.69 ± 0.11 liter/kg	133.5 ± 71.6	PS/1.2 m ²
Linezolid [142]	CVVH (13)	anuric	0.56 ± 0.14 liter/kg	118.6 ± 49.5	PS/0.9 m ²
Daptomycin [143]	CVVH (10)	in vitro study	NA	NA	PS/1.5 m ² AN69/0.9 m ²
Daptomycin [143]	CVVHD (10)	in vitro study	NA	NA	PS/1.5 m ² AN69/0.9 m ²
Clindamycin (no data)					
Rifampicin (no data)					
Azithromycin (no data)					
Clarithromycin (no data)					
Tigecycline (no data)					

Values in parentheses indicate number of patients. Pharmacokinetic data are steady-state data unless otherwise stated. AN69 = Acrylonitrile; CAVH = continuous arteriovenous hemofiltration; CAVHD = continuous arteriovenous hemodialysis; CAVHDF = continuous arteriovenous hemodiafiltration; Cl_{cr} = creatinine clearance; Cl_{urea} = urea clearance; CT = cellulose triacetate; CVVHD = continuous venovenous hemodialysis; ECMO = extracorporeal membrane oxygenation; ESRD = end-stage re-

nal disease; NA = not available; NI = not interpretable; NS = not specified; PA = polyamide; PAN = polyacrylonitrile; PMMA = polymethylmethacrylate; post = postdilution; pre = predilution; PS = polysulfone; U/O = urine output.

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¹ Unless otherwise indicated, values represent ml/min.

ing clinician's workplace. If this is unavailable, the breakpoint for the organism may be helpful so as to avoid the detrimental consequences of underdosing. Knowledge of published pharmacokinetic data (Vd and non-CRRT clearance) on critically ill patients receiving CRRT, the S_c or S_d of the relevant drug (table 3) and the dose and mode of CRRT being employed are essential to formulate the dosing regime (refer to examples given in fig. 2a, b). Several aspects of this recommendation require elaboration. First, for the sake of simplicity, the formula recommended for the calculation of the half-life is based on a single compartment and is therefore not strictly accurate. Second, intravenous infusion of antibacterials with time-dependent killing characteristics is recommended because dose estimation is much simpler and not because of any confirmed effect on outcome. If intermittent bolus doses are used the appropriate maintenance dose can be calculated from:

$$\text{Maintenance dose} = \frac{Vd(1 - e^{-kT}) \times C_{th}}{e^{-kT}}$$

and

$$\text{Loading dose} = \frac{\text{Maintenance dose}}{1 - e^{-kT}}$$

where

$$k = \frac{Cl}{Vd},$$

T = dosing interval (min) and C_{th} = target threshold concentration.

Third, non-CRRT clearance (hepatic and residual renal clearance) needs consideration. Renal clearance needs to be accounted for if residual renal function exists and contributes significantly to total clearance. This is of particular importance if CRRT is being employed for indica-

Fig. 1. Calculation of antibacterial doses based on first principles. Non-CRRT clearance is the sum of nonrenal clearance plus residual renal clearance. Cl_{tot} = Total clearance.

tions other than for AKI (i.e. maintenance of fluid control in massive blood transfusion, dysnatremia and temperature dysregulation). Measurement of creatinine clearance should be considered. In this context, it is important to understand that adjustment for renal clearance based on creatinine clearance assumes that drugs undergo only glomerular filtration and, therefore, this will result in underdosing for drugs with important tubular secretion or overdosing for drugs with tubular reabsorption [10]. Dosing should also take into account the effect of concomitant renal and hepatic failure. For example, the half-life of ciprofloxacin was increased in renal failure, but this was greatly exacerbated by additional hepatic failure [40].

Fourth, when selecting studies from which to obtain S_d , studies which used similar blood and dialysate flows to those being used clinically should be selected. Fifth, if antibacterial concentration assays are available, it is preferable to calculate S_c and S_d in the individual patient from measured blood and effluent concentrations rather than rely on published values, as individual variability is likely to exist. Sixth, antibacterial doses will need to be adjusted when CRRT doses are altered and if the delivered dose of CRRT differs substantially from the prescribed dose due to interruptions in CRRT.

We believe that our approach to dosing has a number of theoretical advantages. It is, however, important to un-

derstand that this method of dosing, like other recommended methods, has not been appropriately validated and like all other methods, it does not take into account inter- and inpatient pharmacokinetic variability. Furthermore, dosing to achieve the pharmacokinetic targets may result in administration of very large doses, depending on the exact pharmacokinetic target chosen (e.g. time above MIC or time above 5 times MIC) and the MIC. It is important that these doses are prescribed bearing in mind that the benefits of optimal killing need to be balanced against the risks of toxicity and that the possibility of using another agent with a more favorable risk:benefit ratio is considered. Where no suitable alternative exists, it may be prudent to restrict doses to the doses approved by regulatory authorities.

The other major weakness of our approach is the variable quality of reporting of pharmacokinetic data in published studies. A recent review indicated that no reports provided the optimal pharmacokinetic dataset and only 29% provided a minimum dataset. Even basic data such as V_d and clearance were missing in approximately 20% of reports [84]. However, as all dosing methods need to be based on these pharmacokinetic data, this weakness applies to all methods.

It is also important to understand that all the dosing recommendations provided, both old and new, give only

Fig. 2. a Calculation of amikacin dose for empirical non-Enterobacteriaceae nosocomial sepsis for a 70-kg patient with residual renal function of 15 ml/min on CVVHDF using an AN69 filter and with targeted total effluent of 35 ml/kg/h. Note that figures are included for illustrative purposes. The dose prescribed should also take into account the risk of toxicity and may need to be reduced to comply with the dose range approved by the regulatory authorities. **b** Calculation of the dose of meropenem for empirical non-Enterobacteriaceae/Enterobacteriaceae/*Staphylococcus* nosocomial sepsis for a 70-kg patient with residual renal function of 20 ml/min on CVVH (postdilution) using an AN69 0.9-m² filter with a targeted ultrafiltration rate of 35 ml/kg/h. Note that figures are included for illustrative purposes. A formula for dose calculation for bolus dosing is given in the text. The dose prescribed should also take into account the risk of toxicity and may need to be reduced to comply with the dose range approved by the regulatory authorities. Cl_{tot} = Total clearance; Cl_{HF} = hemofiltration clearance; Cl_{CVVH} = CVVH clearance.

Table 5. A complete dataset recommended for the pharmacokinetic study of patients with antibacterials receiving CRRT

Category	Parameters
Patient characteristics	Age, weight, residual renal function, hepatic function, and severity of illness
Drug data	Target concentration and dose recommendation
Pharmacokinetics	Vd, protein binding, serum albumin, total clearance, CRRT clearance and non-CRRT clearance
CRRT	Hemofilter membrane material and surface area CVVH: if predilution, S_c , ultrafiltration rate, blood flow rate, hematocrit, and predilution replacement rate; if post-dilution, S_c and ultrafiltration rate CVVHD: S_d , dialysate rate CVVHDF: S_c/S_d , ultrafiltration rate and dialysate rate

estimated doses and where possible doses should be further adjusted according to measured blood concentrations. Therapeutic drug monitoring has been recommended not only for more toxic agents such as vancomycin and aminoglycosides, but to increase the likelihood of appropriately high dosing of β -lactams [89]. Although measured drug concentrations can be used to guide empiric increases or decreases in doses, optimal dose adjustment still requires knowledge of the factors discussed above. For example, a measurement showing that the concentration of a β -lactam is below the threshold concentration early in the dosing interval is helpful in indicating that a dose increase is required, but knowledge of Vd and clearance is still necessary in order to make the optimal dose adjustment. However, with an appropriate understanding of the issues therapeutic drug monitoring can be used to enhance the approach that we have advocated. For example, by measuring blood and effluent concentrations, S_c or S_d and hence CRRT clearance can be

calculated, or by measuring blood and urine concentrations and measuring urine volume, renal clearance can be calculated. As this method would provide individualized clearance values, it would eliminate many of the problems resulting from the variability of filters, interpatient differences and inadequacy of data reported in published studies. However, the value and cost-effectiveness of antibiotic drug monitoring have yet to be demonstrated, and these assays are not available to most clinicians at present.

Although for some classes of antibiotics appropriate pharmacokinetic targets have been established, this is not the case for all agents (table 2), and for some drugs that are concentrated in tissues (e.g. macrolides, ketolides and azalides), blood concentrations may not be a useful guide [90]. In these cases our proposed method of calculating an appropriate dose is not useful.

Antibiotic Dosing in the Future

We have presented a method for the calculation of antibiotic dosing that allows appropriate dose delivery to critically ill patients receiving CRRT. The calculation is based on first principles, but relies on the availability of pharmacokinetic data derived from critically ill patients receiving CRRT. Such data are not universally available, partly because of a paucity of investigative studies, especially for older antibiotics such as amoxicillin, ampicillin, flucloxacillin and gentamicin, but also because published studies have frequently failed to report sufficient pharmacokinetic data [84]. Based on the high rate of incomplete reporting, even for important parameters such as Vd, CRRT drug clearance and protein binding, we are of the opinion that a complete dataset such as that previously recommended (table 5) should be reported in all newly published studies as a basic standard.

Finally, therapeutic drug monitoring may alleviate much of the uncertainty of dosing antibiotics in CRRT.

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