Principles of antibacterial dosing in continuous renal replacement therapy

Gordon Choi, MBBS, FJFICM; Charles D. Gomersall, MBBS, FJFICM; Qi Tian, PhD; Gavin M. Joynt, MBBCh, FJFICM; Ross Freebairn, MBChB, FJFICM; Jeffrey Lipman, MBBCh, FJFICM, MD

Objectives: **To outline the concepts involved in optimizing antibacterial dosing in critically ill patients with acute renal failure undergoing continuous renal replacement therapy (CRRT), provide a strategy for optimizing dosing, and summarize the data required to implement the strategy.**

Data Sources: **MEDLINE search from February 1986 to 2008.**

Data Extraction and Synthesis: **Optimal dosing of antibacterials is dependent on achieving pharmacokinetic targets associated with maximal killing of bacteria and improved outcomes. The initial dose is dependent on the volume of distribution. Maintenance doses are dependent on clearance. Both should be adjusted according to the pharmacokinetic target associated with optimal bacterial killing, when known. The volume of distribution of some antibacterials is altered by critical illness or acute renal failure or both. Clearance by CRRT is dependent on the dose and mode of CRRT and the sieving or saturation coefficient of the drug. Both sieving and saturation coefficient are related to the plasma protein binding and thus may be altered in renal failure.**

Conclusions: **Appropriate dose calculation requires knowledge of the pharmacokinetic target and the usual minimum inhibitory concentration of the suspected organism in the patient's locality (or if unavailable, the break point for the organism), published pharmacokinetic data (volume of distribution, non-CRRT clearance) on critically ill patients receiving CRRT (which may differ substantially from noncritically ill patients or those without renal failure), the sieving or saturation coefficient of the relevant drug in critically ill patients, the dose and mode of CRRT being used, and the actual dose of CRRT that is delivered. This large number of variables results in considerable inter- and intrapatient heterogeneity in dose requirements. This article provides basic principles and relevant data to guide the clinician in prescribing individualized dosing regimes. (Crit Care Med 2009; 37:2268–2282)**

KEY WORDS: antibacterial agents; critical illness; kidney failure; acute; renal replacement therapy; pharmacokinetics; pharmacodynamics

The combination of sepsis and acute renal failure is common in the critically ill (1, 2) and is associated with a high mortality (3). Optimal treatment is essential to maximize survival. Although underdosing of antibacterials may result in decreased bacterial killing, failure of clinical resolution, and increased resistance, overdosing may result in toxicity (4). Unlike many other drugs, the dose of antibacterials cannot be titrated to effect as changes in clinical markers usually occur over days (5). Instead, dosing is adjusted to achieve pharmacokinetic targets that are associated with improved outcome. These targets are related to *in vitro* inhibitory concentrations for relevant organisms and the class of antibacterial. Correct dosing, therefore, requires consideration of several factors.

First, the pharmacokinetics of antibacterials in critically ill patients with acute renal failure are substantially different from those encountered in less ill subjects. Alterations in protein binding (PB) and total body water affect pharmacokinetic parameters such as volume of distribution and renal clearance by artificial modes. Additionally, variation in the efficiency of continuous renal replacement therapy (CRRT) among institutions, as well as inter- and intrapatient variation in dose of CRRT, may lead to substantial variation in antibacterial clearance. This is, of course, only relevant to those drugs that are eliminated by CRRT, which are those that usually undergo significant (>25% to 30%) renal elimination (6). Last, there are well-known differences among classes of antibacterials in the relationship between pharmacokinetic parameters and pharmacodynamic characteristics. Dosing regimes should, therefore, be individualized and take all of these factors into account (7).

This review aims to summarize the important pharmacokinetic and pharmacodynamic considerations encountered in critically ill patients receiving CRRT and antibacterial therapy, and provides some practical recommendations to assist in individualized dosage. To aid the reader, a list of frequently used abbreviations is given in Table 1.

Pharmacokinetic–Pharmacodynamic Relationships

Appropriate antibacterial dosing requires implementation of sound pharmacokinetic–pharmacodynamic principles.

From the Department of Anaesthesia and Intensive Care (GC, CDG, QT, GMJ, RCF), The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong, China; and Burns, Trauma and Critical Care Research Centre (JL), University of Queensland, Royal Brisbane and Women's Hospital, Herston, Queensland, Australia.

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For information regarding this article, E-mail: j.lipman@uq.edu.au

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Table 1. Frequently used abbreviations

Abbreviation	Meaning
AUC_{24}	Area under the concentration-time curve over 24 hrs
C_{max}	Maximum post distribution plasma concentration
Cl_{CVVH}	Clearance by continuous venovenous hemofiltration
Cl_{CVVHD}	Clearance by continuous venovenous hemodialysis
Cl_{CVVHDF}	Clearance by continuous venovenous hemodiafiltration
CRRT	Continuous renal replacement therapy
CVVH	Continuous venovenous hemofiltration
CVVHD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
Cl_{tot}	Total clearance
MIC	Minimum inhibitory concentration
PB	Plasma protein binding
Q_b	Blood flow rate
Q_d	Dialysate flow rate
Q_f	Ultrafiltrate flow rate
Q_{rep}	Replacement fluid flow rate
Sc	Sieving coefficient
S_d	Saturation coefficient
Vd	Volume of distribution

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

Antibacterial	Killing Characteristics	Pharmacokinetic Targets
Aminoglycosides	Concentration dependent	C_{max}:MIC 8–10 (17)
Metronidazole	Concentration dependent	Not established
Fluoroquinolones	Concentration dependent	C_{max}:MIC 6–8, AUC_{24}:MIC 100–125 (Gram negatives), 34 (*Streptococcus pneumoniae*) (62, 74)
Vancomycin	Concentration dependent	AUC_{24}:MIC ≥400 (vs. *Staphylococcus aureus*) (75)
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 (73)
Linezolid	Concentration dependent	AUC_{24}:MIC 50 (*Streptococcus pneumoniae*), AUC_{24}:MIC 82 (*Staphylococcus aureus*) (76)
Beta lactams	Time dependent	40–100% of dosing interval >MIC or 40–100% of dosing interval >5 times MIC (9)

AUC_{24}, area under concentration-time curve over 24 hrs; C_{max}, post distribution peak concentration; MIC, minimum inhibitory concentration.

These have recently been reviewed (8) . In brief, the killing characteristics and pharmacokinetic targets associated with optimal bacterial killing vary among antibiotics (Table 2). Killing characteristics can be described as time dependent (or nonconcentration dependent) and concentration dependent. For agents that exhibit time-dependent killing (e.g., β-lactams), killing is related to the time during which the blood concentration is above a threshold concentration. Appropriate values for both the threshold concentration and the time are controversial, with recommended concentrations ranging from one to five times minimum inhibitory concentration (MIC) (9) and the time ranging from 40% to 100% of the dosing interval (10). The use of continuous infusions of time-dependent killing antibacterials may be superior in maximizing time above the threshold concentration without unnecessarily high peak concentrations (11–14); however, data demonstrating improved patient outcome are scarce (15).

For agents that demonstrate concentration-dependent killing, optimal killing may be associated with the postdistribution peak plasma concentration (C_{max}): MIC ratio (e.g., aminoglycosides), the ratio of the area under the plasma concentration–time curve during a 24-hour period (AUC_{24}) to MIC (AUC_{24}:MIC) (e.g., linezolid), or both (e.g., fluoroquinolones). For aminoglycosides, maintaining a fixed dosage with prolonged dosing interval not only increases the efficacy of the treatment but also minimizes toxicity (8, 16, 17).

Basic Principles of CRRT

Modern CRRT is performed as a venovenous procedure as continuous venovenous hemofiltration (CVVH), hemodialysis (CVVHD), or hemodiafiltration (CVVHDF) (18–20). Being a relatively slow and continuous process, there is a risk that the delivered dose of CRRT may be substantially less than the prescribed dose in the intensive care unit because of unnoticed interruptions in treatment (e.g., transport out of the intensive care unit for investigations or surgery, or frequent filter clogging).

Hemofiltration

Hemofiltration uses convective removal. Plasma water passes across the filter membrane down a (predominantly hydrostatic) pressure gradient dragging solute with it (Fig. 1, *A* and *B*). For most commonly used antibacterials, which include large molecules such as vancomycin (1448 Da) and teicoplanin (1878 Da), convective transport across commonly used modern membranes (pore sizes 10,000–30,000 Da) is independent of molecular weight (21, 22). The ability of a drug to pass through the membrane is expressed as the sieving coefficient (S_c): the ratio of drug concentration in the ultrafiltrate to plasma.

$$S_c = \frac{[\text{Drug}]_{\text{ultrafiltrate}}}{[\text{Drug}]_{\text{plasma}}}$$

In general, S_c ranges from 0 to 1. Drug PB is the main determinant of S_c and it has been suggested that S_c can be estimated from published values of PB, such that $S_c = 1 - \text{PB}$. Measured S_c and S_c estimated from published values of PB are correlated (23). However, as discussed below, PB 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.

Replacement fluid can be added to the circuit either before the filter (predilution) or after (postdilution) (Fig. 1, *A* and *B*). In postdilution mode, drug clearance

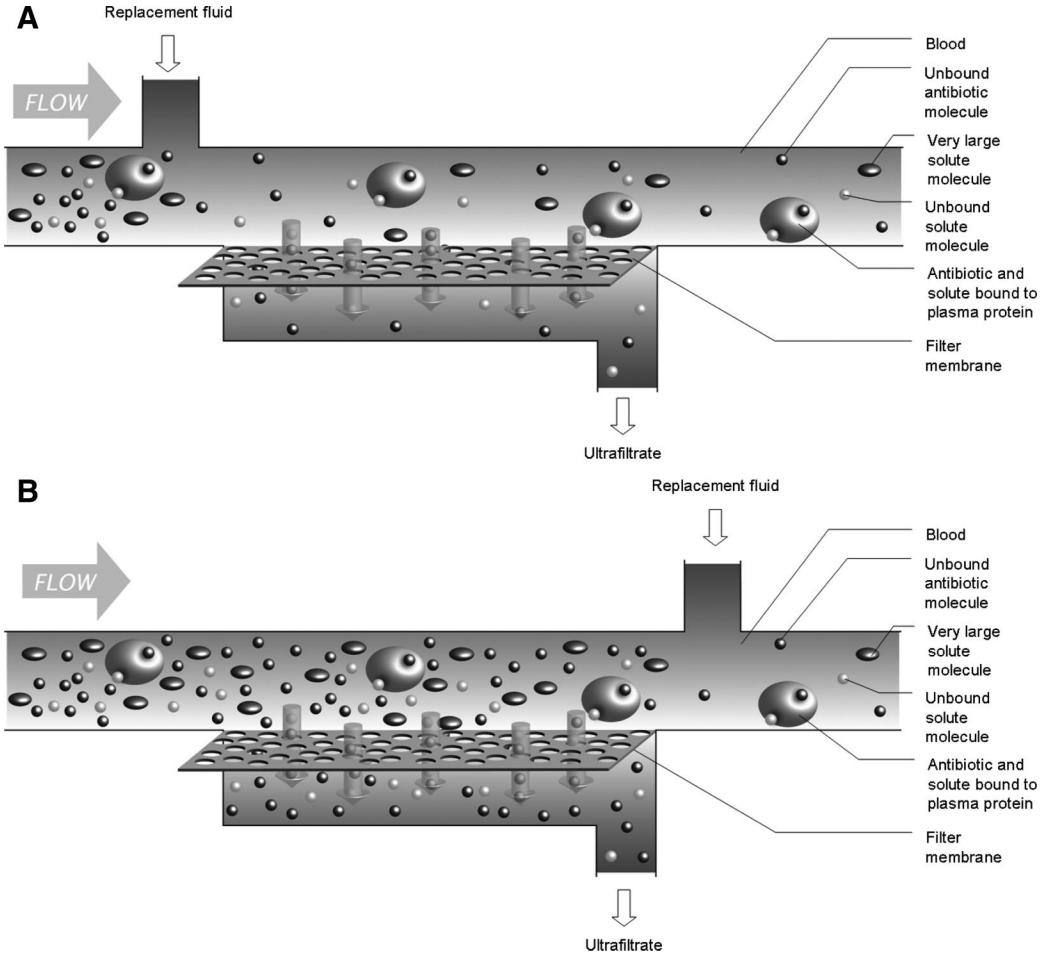

Figure 1. *A*, Hemofiltration (continuous venovenous hemofiltration) (predilution). Dilution of blood with replacement fluid before the blood enters the filter results in a fall in concentration in the filter and hence a reduction in efficiency of solute removal. Protein bound molecules are unable to cross the membrane. *B*, Hemofiltration (continuous venovenous hemofiltration) (postdilution). Reproduced with permission from ICU web (www.aic.cuhk.edu.hk/web8).

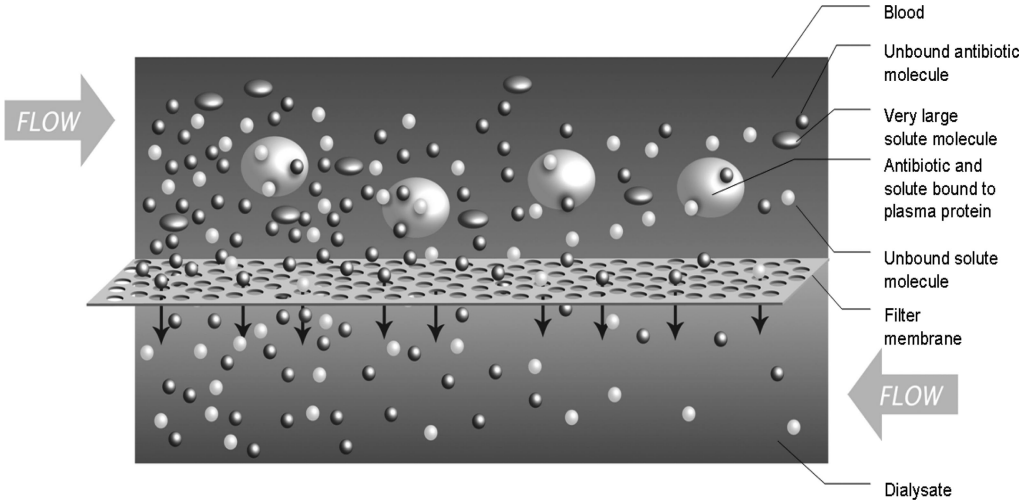

Figure 2. Continuous venovenous hemodialysis. The countercurrent flow maintains a concentration gradient across the membrane. Protein bound molecules are unable to cross the membrane. Reproduced with permission from ICU web (www.aic.cuhk.edu.hk/web8).

depends on ultrafiltration rate and S_c such that:

$$CI_{CVVH}(post) = Q_f \times S_c$$

In predilution mode (Fig. 1*A*), the plasma entering the hemofilter is diluted by replacement fluid, so drug clearance will be lowered by a correction factor (CF) determined by blood flow rate (Q_b) and predilution replacement rate (Q_{rep}). Drug clearance in predilution mode can be calculated as:

$$Cl_{CVVH}(pre) = Q_f \times S_c \times CF,$$

where $CF = Q_b/(Q_b + Q_{rep})$

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 (29) and an *in vivo* study that revealed a clinically significant reduction in clearance during predilution CVVH (30). In addition, the ratio of predilution:postdilution influences S_c as well as clearance. For vancomycin, S_c steadily decreased as the proportion of predilution decreased (30).

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 ultrafiltration rate. As the expected magnitude of change in ultrafiltration is substantially greater than the variability of S_c, ultrafiltration is the more important consideration.

Hemodialysis

Hemodialysis uses diffusion of solute across filter membrane down a concentration gradient between plasma and dialysate (Fig. 2). Equilibration across the filter membrane is dependent on the interaction among molecular weight, blood flow, and dialysate flow. Given that the dialysate flow rate in CVVHD and CVVHDF is relatively low compared with blood flow rate (31), neither blood flow nor molecular size is an important factor in clearance of most commonly used antibacterials.

The ability of a drug to diffuse through the filter membrane is most simply expressed as the saturation coefficient (S_d):

$$S_d = \frac{[Drug]_{dialysate}}{[Drug]_{plasma}}$$

Again, PB is the main determinant of S_d. Similar to sieving coefficient, S_d is membrane specific, subject to drug–membrane interactions and flux properties, and ranges in value from 0 to 1. In usual clinical practice, blood flow is so much greater than dialysate flow that complete saturation occurs and drug clearance is effectively dependent on dialysate flow rate (Q_d) and S_d:

$$Cl_{CVVHD} \approx Q_d \times S_d$$

Hemodiafiltration

Hemodiafiltration uses both convection and diffusion to eliminate drugs. In general, drug clearance in CVVHDF may be estimated as:

$$Cl_{CVVHD} = (Q_f + Q_d) \times S_d$$

However, during CVVHDF the two processes interact to reduce each other's

Table 3. Factors affecting elimination of antibacterials in patients receiving continuous renal replacement therapy CRRT

Factors	Notes
Pharmacokinetic factors	
Residual renal elimination	
Nonrenal elimination	May be increased in acute renal failure but may be decreased by concomitant hepatic failure
Volume of distribution	Increase in volume of distribution results in need for larger loading dose and reduces efficacy of removal by CRRT
Protein binding	Only the unbound fraction is removed by CRRT
CRRT factors	
Mode of CRRT	
Dose of CRRT delivered	In clinical practice effluent volume is the most important CRRT variable in determining drug elimination. Effluent volume is dependent on both effluent flow and duration of CRRT
Blood flow rate	Within usual clinical limits varying blood flow has little effect on elimination
Filter material	Sieving coefficient may vary between different filter materials for some antibacterials
Surface area	This has no direct effect on elimination

Table 4. Currently available methods of estimating antibacterial dose in patients receiving CRRT

Method	Authors	Mode of CRRT	Formula	Assumptions
1	Golper et al (23)	CVVH	$D = C_{SS} \times UBF \times UFR \times I$	Assays to measure antibacterial concentration are widely available Sieving coefficient is equal to unbound fraction of drug
2	Bugge et al (51)	CVVHDF	$D = D_N\left(P_x + (1 - P_x)\frac{Cl_{CRtot}}{Cl_{CRn}}\right)$	Assays to measure antibacterial concentration are widely available Sieving coefficient is equal to unbound fraction of drug Normal dose achieves pharmacokinetic targets associated with optimal killing
3	Schetz et al (6)	CVVH	$D = D_N\left(\frac{Cl_{NR} + (UFR \times S_c)}{Cl_N}\right)$	Normal dose achieves pharmacokinetic targets associated with optimal killing
4	Schetz et al (6)	All modes	$D = \frac{D_{anuria}}{1 - \left(\frac{Cl_{EC}}{Cl_{EC} + Cl_{NR} + Cl_R}\right)}$	Assays to measure antibacterial concentration are widely available Dose given to anuric patients achieves pharmacokinetic targets associated with optimal killing

C_{ss}, measured blood concentration at steady state; Cl_{ANUR}, drug clearance in anuric patient; 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_R renal 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); S_c, sieving coefficient; UBF, unbound fraction; UFR, ultrafiltration rate.

Table 5. Pharmacokinetic data for antibacterials commonly used in the intensive care unit in patients receiving CRRT

Drug (Reference)	Mode of CRRT (No Patients)	Residual Renal Function	Volume of Distribution	Non-CRRT Clearance (mL/min)	Membrane/Surface Area
Penicillins					
Ampicillin (no data)					
Amoxicillin (77)	CVVH (12)	U/O <400 mL/12 hr	NS	NS	CT/1.9 m^2
Piperacillin (78)	CVVH (6)	Four anuric patients. Two patients U/O <400 mL/24 hr	0.48 ± 0.24 L/kg	NS	PS/0.5 m^2
Piperacillin (78)	CVVH (4)	Three anuric patients. One patient U/O = 220 mL/24 hr	0.14 ± 0.07 L/kg	NS	PS/0.5 m^2
Piperacillin (79)	CAVHD (12)	Clurea: 18.4 ± 2.3 mL/min	25.8 ± 3.8 L	34.9 ± 21.2	AN69/0.43 m^2
Piperacillin—Tazobactam (80)	CVVH (4)	Clcr: 8.67 ± 2.31 mL/min	Piperacillin: 21.0 ± 11.7 L, Tazobactam: 18.9 ± 7.1 L	Piperacillin: 38.55, Tazobactam: 29.5	AN69/0.9 m^2
Piperacillin—Tazobactam (80)	CVVH (5)	Clcr: 25.20 ± 7.73 mL/min	Piperacillin: 26.8 ± 19.8 L, Tazobactam: 21.6 ± 3.0 L	Piperacillin: 78.4, Tazobactam: 46.3	AN69/0.9 m^2
Piperacillin—Tazobactam (81)	CVVHD (8)	Anuric	Piperacillin: 0.31 Clavulanate 0.07 L/kg, Tazobactam: 0.24 ± 0.09 L/kg	Piperacillin: 49.5 ± 60.1 mL/min, Tazobactam: 23.7 ± 14.9 mL/min	AN69/0.6 m^2
Ticarcillin—clavulanate (82)	CVVH (3)	Two patients anuric. One patient U/O >2 L/day	Ticarcillin: 0.26 L/kg (n = 2, with ECMO), 0.25 L/kg (n = 1, without ECMO), Clavulanate: 0.86 L/kg (n = 2, with ECMO), 0.33 L/kg (n = 1, without ECMO)	Ticarcillin: 5.75 ml/min (n = 2, with ECMO), 40.83 ml/min (n = 1, without ECMO), Clavulanate: 61.75 ml/min (n = 2, with ECMO), 186.8 ml/min (n = 1, without ECMO)	PS/0.25 m^2
Flucloxacillin (77)	CVVH (5)	U/O <400 mL/12 hr	NS	NS	CT/1.9 m^2
Flucloxacillin (83)	CVVH (10)	Anuric	0.54 ± 0.43 L/kg	106.9 ml/min	PA/0.7 m^2
Oxacillin (no data)					
Nafcillin (no data)					
Cloxacillin (no data)					
Cephalosporins					
Cefuroxime (84)	CAVHD (12)	NS	22.8 ± 9.2 L	1.5 mL/min	AN69/0.43 m^2
Cefuroxime (85)	CAVH (3)	Clcr <1 mL/min	21 ± 2.5 L	21 ± 6.6 mL/min	PS/0.6 m^2
Cefotaxime (no data)					
Ceftazidime (84)	CAVHD (9)	NS	31.1 ± 14.6 L (5)	15.15 mL/min	AN69/0.43 m^2
Ceftazidime (86)	CVVH (12)	Anuric	0.41 ± 0.16 L/kg	66.57 ± 12.90 mL/min	PS/0.7 m^2
Ceftazidime (87)	CVVH/CVVHD (8)	Clcr <20 mL/min	NS	NS	AN69/0.6 m^2, PMMA/2.1 m^2, PS/0.65 m^2
Ceftazidime (88)	CVVHDF (7)	Clcr ≤ 5 mL/min	0.25 ± 0.09 L/kg	28.9 ± 5.6 mL/min	AN69/0.6 m^2
Ceftazidime (47)	CVVHDF (2)	Clcr = 0 mL/min	0.46 L/kg	24.95 ml/min	AN69/0.9 m^2
Ceftazidime (77)	CVVH (7)	U/O <400 mL/12 hr	NS	NS	CT/1.9 m^2
Ceftriaxone (89)	CVVH (6)	Clcr <10 mL/min	0.42 ± 0.21 L/kg	22.7 ± 19.1 mL/min	PA/1.4 m^2
Ceftriaxone (87)	CVVH (5)	ESRD	NS	NS	AN69/0.6 m^2
Ceftriaxone (87)	CVVH (5)	ESRD	NS	NS	PMMA/2.1 m^2
Ceftriaxone (87)	CVVH (5)	ESRD	NS	NS	PS/0.65 m^2
Cefepime (77)	CVVH (2)	Clcr = 29 mL/min (1)	0.65 L/kg	NI	AN69/0.9 m^2
Cefepime (90)	CVVHDF (2)	Clcr <10 mL/min, Clcr = 35 mL/min	0.6 L/kg	NI	AN69/0.9 m^2, PS/1.4 m^2
Cefepime (91)	CVVH (5)	U/O <155 mL/24 hr	0.46 ± 0.14 L/kg	23 ml/min	AN69/0.6 m^2
Cefepime (91)	CVVHDF (7)	U/O <67 mL/24 hr	0.34 ± 0.1 L/kg	21 ml/min	AN69/0.6 m^2
Cefoperazone (no data)					
Monobactams					
Aztreonam (no data)					
Carbapenems					
Imipenem (37)	CVVH (6)	Two anuric patients. Four patients U/O <43 mL/24 hr	0.36 ± 0.10 L/kg	109 ± 24 mL/min	AN69/0.6 m^2
Imipenem (37)	CVVHDF (6)	Two anuric patients. Four patients U/O <135 mL/24 hr	0.37 ± 0.13 L/kg	120 ± 32 mL/min	AN69/0.6 m^2
Imipenem—Cilastatin (92)	CAVH (6)	Two anuric patients. Four patients U/O <350 mL/24 hr	Imipenem: 0.29 ± 0.03 L/kg Cilastatin: 0.27 ± 0.07 L/kg	Imipenem: 108.5 ± 29.6 ml/min, Cilastatin: 20.6 ± 30.3 ml/min	PS/NS
Imipenem—Cilastatin (93)	CVVH (12)	Ten anuric patients. Two patients U/O = 200 mL/8 hr	Imipenem: 24.3 ± 7.7 L, Cilastatin: 19.6 ± 7.3 L	Imipenem: 90.8 ± 26.3 ml/min, Cilastatin: 13.2 ± 13.9 ml/min	AN69/NS
Imipenem—Cilastatin (94)	CVVHD (6)	Anuric	Imipenem: 0.37 ± 0.16 L/kg, Cilastatin: 0.26 ± 0.09 L/kg	Imipenem: 70.6 ± 18.1 ml/min, Cilastatin: 18.0 ± 9.9 ml/min	PAN/0.5 m^2
Imipenem—Cilastatin (95)	CAVH or CAVHDF (8)	NS	NS	NS	AN69/0.6 m^2
Imipenem (96)	CVVH (7)	NS	0.33 ± 0.09 L/kg	NI	PS/0.25 m^2
Meropenem (39)	CVVH (9)	Anuric	0.36 ± 0.07 L/kg	94.0 ± 26.9 mL/min	PS/0.43 m^2
Meropenem (40)	CVVHDF (9)	Anuric	0.26 ± 0.09 L/kg	22.7 ml/min	AN69/0.9 m^2
Meropenem (97)	CVVH (9)	Clcr = 1.3 mL/min	12.4 ± 1.8 L	29.9 ± 5.4 mL/min	AN69/NS
Meropenem (41)	CVVH (5)	NS	0.38 ± 0.12 L/kg	NI	AN69/0.9 m^2
Meropenem (41)	CVVHDF (5)	NS	0.31 ± 0.08 L/kg	NI	AN69/0.9 m^2
Meropenem (42)	CVVH (8)	U/O <500 mL/24 hr	0.28 ± 0.07 L/kg	58.52 ± 24.46 mL/min	AN69/0.9 m^2

Table 5.—*Continued*

S_c (Pre)	S_c (Post)	S_d	Dose Recommended by Authors	Total Effluent Rate (Range, Unless Otherwise Specified)	Remarks
0.71 ± 0.16. Route of dilution NS		NA	NS	Mean ± SD 29 ± 7 mL/kg/hr	
NS	NS	NS	4 g 12 hourly	0.76 ± 0.20–0.88 ± 0.18 L/hr	First-dose pharmacokinetics
NS	NS	NS	4 g 12 hourly	0.50 ± 0.08–0.72 ± 0.14 L/hr	
NA	NA	0.71 ± 0.21	150% of dose for anuric patients	Mean ± SD 1.22 ± 0.09 L/hr	
Piperacillin: 0.42 ± 0.25, Tazobactam: 0.76 ± 0.26	NA	NA	NS	Mean ± SD 1.63 ± 0.47 L/hr	
Piperacillin: 0.38 ± 0.37, Tazobactam: 0.73 ± 0.32	NA	NA	NS	Mean ± SD 1.82 ± 0.26 L/hr	
NA	NA	Piperacillin: 0.87 ± 0.21, Tazobactam: 0.64 ± 0.19	NS	1.58–1.70 L/hr	
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 L/hr	Children (2 patients receiving concomitant ECMO, 1 patient without ECMO U/O >2 L/day)
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/hr	
NA	0.21 ± 0.09	NA	4 g 8 hourly	Mean ± SD 3.42 ± 0.54 L/hr	
NA	NA	0.90 ± 0.33	500–750 mg 12 hourly	1–2 L/hr	
NA	NA	NA	Initial 1.5 g, then 750 mg 20–24 hourly	Mean ± SD 0.85 ± 0.11 L/hr	Not critically ill
NA	NA	0.86 ± 0.08	500 mg 12 hourly	1–2 L/hr	
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 L/hr	
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 L/hr CVVHD 0.5–2 L/hr	
NA	NA	0.81 ± 0.11	Initial 2 g, then 3 g daily by continuous infusion	2.5 L/hr	Predilution
NA	NA	0.9	NS	1.5–2 L/hr	Predilution
0.87 ± 0.46. Route of dilution NS		NA	NS	Mean ± SD 25 ± 7 mL/kg/hr	
NA	0.69 ± 0.39	NA	2 g daily	1.2–1.8 L/hr	Ceftriaxone not recommended for patients given calcium containing intravenous solutions
0.48 ± 0.13. No replacement fluid administered		NA	NS	0.5–1 L/hr	
0.86 ± 0.33. No replacement fluid administered		NA	NS	0.5–1 L/hr	
0.82 ± 0.22. No replacement fluid administered		NA	NS	0.5–1 L/hr	
0.62	NA	NA	2 g 8 hourly	1.0–2.1 L/hr	
NA	NA	AN69 0.83, PS 0.97	2 g 8 hourly	2.14–2.5 L/hr	Predilution
NA	0.86 ± 0.04	NA	2–4 g daily	0.54–1.14 L/hr	
NA	NA	0.78 ± 0.10	2–4 g daily	1.78–2.35 L/hr	
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 L/hr	
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 L/hr	
1.16/0.7 Route of dilution NS		NA	NS	0.24–7.9 L/hr	
Imipenem: 1.2 ± 0.1, Cilastatin: 0.8 ± 0.2. Route of dilution NS		NA	0.5 g daily	1.1–1.2 L/hr	
NA	NA	NS	0.5 g each of imipenem and cilastatin 12 hourly	1.26–1.38 L/hr	
Imipenem: 1.05 ± 0.19, Cilastatin: 0.68 ± 0.08	NA	NS	0.5 g 12 hourly	1–3 L/hr	
Route of dilution NS		NA	0.5 g 6–8 hourly	1 L/hr	
NA	1.09 ± 0.10	NA	1 g 8 hourly	Mean ± SD 2.7 ± 0.4 L/hr	First-dose pharmacokinetics
NA	NA	NS	1 g 12 hourly	1.6–1.9 L/hr	
1.17 ± 0.11. Route of dilution NS		NA	1 g daily	1.1–1.15 L/hr	
NA	0.95 ± 0.03	NA	1 g 12 hourly	1.0–2.0 L/hr	
NA	NA	0.92 ± 0.08	1 g 12 hourly	2.0–3.0 L/hr	
0.91 ± 0.10		NA	500 mg 12 hourly	1.6 L/hr	

(*Continued*)

Table 5.—*Continued*

Drug (Reference)	Mode of CRRT (No Patients)	Residual Renal Function	Volume of Distribution	Non-CRRT Clearance (mL/min)	Membrane/Surface Area
Meropenem (98)	CVVHDF (7)	Clcr = 1.14 mL/min	0.57 ± 0.29 L/kg	123.26 ml/min	AN69/1.4 m^2 PS/0.9 m^2
Meropenem (98)	CVVH (4)	Clcr = 12.5 ± 12.1 mL/min	0.38 ± 0.07 L/kg	114.38 ± 51.78 mL/min	AN69/1.4 m^2 PS/0.9 m^2
Meropenem (98)	CVVHDF (3)	Clcr = 24.8 ± 18.1 mL/min	0.36 ± 0.14 L/kg	85.92 ± 75.83 mL/min	AN69/1.4 m^2 PS/0.9 m^2
Meropenem (99)	CVVHDF (6)	NS	Median (IQR) 32.3 (28.9–40.7) L	NS	PS/1.4 m^2
Meropenem (99)	CVVHDF (6)	NS	NS	NS	PS/1.4 m^2
Meropenem (44)	CVVH (5)	One patient anuric. Four patients U/O <50 mL/24 hr	0.37 ± 0.15 L/kg	59 ± 17.7 mL/min	PAN/0.6 m^2
Meropenem (100)	CVVHDF (12)	Ten patients anuric. Two patients U/O <180 mL/24 hr	0.49 ± 0.16 L/kg	46.96 ± 29.61 mL/min	AN69/0.9 m^2
Ertapenem (no data)					
Quinolones					
Moxifloxacin (101)	CVVHDF (9)	Anuric	270 ± 133 L	291 mL/min	AN69/0.9 m^2
Levofloxacin (28)	CVVH (12)	Anuric	4.3 ± 1.8 L/kg	NS	PA/0.7 m^2
Levofloxacin (26)	CVVH (4)	One patient anuric. Three patients U/O ≤40 mL/24 hr	1.05 L/kg	30.8 mL/min	AN69/0.6 m^2
Levofloxacin (26)	CVVHDF (6)	U/O ≤128 mL/24 hr	1.0 L/kg	29.5 mL/min	AN69/0.6 m^2
Levofloxacin (25)	CVVHDF (6)	Clcr <10 mL/min (6)	1.51 ± 0.52 L/kg	28.0 ± 33.7 mL/min	AN69/0.9 m^2
Levofloxacin (25)	CVVH (6)	Clcr <10 mL/min	1.42 ± 0.42 L/kg	32.2 ± 27.5 mL/min	AN69/0.9 m^2
Levofloxacin (27)	CVVH (4)	Anuric	1.02 ± 0.66 L/kg	26.3 ± 14.8 mL/min	AN69/0.9 m^2
Ciprofloxacin (26)	CVVH (5)	One patient anuric. Four patients U/O ≤155 mL/24 hr	1.12 L/kg	72 mL/min	AN69/0.6 m^2
Ciprofloxacin (26)	CVVHDF (5)	Two patients anuric. Three patients U/O ≤90 mL/24 hr	0.96 L/kg	125.2 mL/min	AN69/0.6 m^2
Ciprofloxacin (36)	CVVHDF (6)	NS	1.56 ± 0.35 L/kg	NI	AN69/NS
Ciprofloxacin (77)	CVVH (16)	U/O <400 mL/12 hr	NS	NS	CT/1.9 m^2
Ciprofloxacin (102)	CVVHDF (1)	NS	NS	NS	PA/0.6 m^2
Glycopeptides					
Vancomycin (78)	CVVH (6)	U/O<400 mL/12 hr	NS	NS	CT/1.9 m^2
Vancomycin (103)	CVVH (5)	End-stage renal failure	NA	NS	AN69/0.6 m^2, PMMA/2.1 m^2, PS/0.65 m^2
Vancomycin (104)	CVVHDF (10)	NS	49.7 ± 29.1 L	NI	AN69/NS
Vancomycin (105)	CVVH (10)	Anuric	0.55 ± 0.12 L/kg	16.2 ± 7.0 mL/min (range, 3.8–23.3)	PS/0.25 m^2
Vancomycin (106)	CVVH (2)	U/O ≤46 mL/24 hr	41.7 L, 55.8 L	10 mL/min	PAN/0.6 m^2
Vancomycin (30)	CVVH (7)	NS	NS	NS	AN69/1.6 m^2
Teicoplanin (107)	CVVHDF (3)	Clcr = 2.41 mL/min	1.23 ± 0.77 L/kg	7.84 ml/min	NS
Teicoplanin (108)	CVVH (1)	Clcr = 35 mL/min	NS	NS	AN69/0.9 m^2
Teicoplanin (109)	CVVHD (5)	Clcr 5.8 ± 2.7 mL/min	0.93 ± 0.42 L/kg	NS	AN69/0.6 m^2
Aminoglycosides					
Gentamicin (110)	CAVH (4)	Three patients U/O <572 mL/24 hr. One patient U/O NS	0.36 ± 0.09 L/kg	9.55 ± 9.82 mL/min	PS/0.25 m^2
Gentamicin (111)	CAVHDF (5)	Clcr = 2.8 mL/min	NS	15.26 ± 7.09 mL/min	PAN/0.43 m^2
Netilmicin (112)	CVVHDF (6)	Clcr = 22.3 ± 6.2 mL/min	24.92 ± 5.96 L	NS	AN69/0.6 m^2
Amikacin (113)	CVVH (5)	Anuric	35 ± 7.5 L	22.6 mL/min	PS/0.6 m^2
Amikacin (114)	CVVHDF (6)	NS	0.47 ± 0.08 L/kg	NS	AN69/NS
Tobramycin (110)	CAVH (4)	Two patients anuric. Two patients U/O <32 mL/24 hr	0.28 ± 0.08 L/kg	6.83 ± 3.22 mL/min	PS/0.25 m^2
Miscellaneous					
Colistin (115)	CVVHDF (1)	Multiple organ failure	10.9 L	37.5 mL/min	AN69/NS
Linezolid (116)	CVVH (2)	U/O <200 mL/24 hr	0.485 L/kg	NS	AN69XT/1.65 m^2
Linezolid (117)	CVVH (2)	Anuric	1.02 L/kg	36.8 mL/min	PS/1.25 m^2
Linezolid (118)	CVVH (7)	Anuric	0.69 ± 0.11 L/kg	133.5 ± 71.6 mL/min	PS/1.2 m^2
Linezolid (118)	CVVH (13)	Anuric	0.56 ± 0.14 L/kg	118.6 ± 49.5 mL/min	PS/0.9 m^2
Daptomycin (119)	CVVH (10)	*In vitro* study	NA	NA	PS/1.5 m^2, AN69/0.9 m^2

Table 5.—*Continued*

S_c (Pre)	S_c (Post)	S_d	Dose Recommended by Authors	Total Effluent Rate (Range, Unless Otherwise Specified)	Remarks
NA	NA	AN69 0.76 ± 0.15, PS 0.76 ± 0.08	NS	1.5–2.5 L/hr	Predilution
AN69 0.80 ± 0.15, PS 1.01	NA	NA	NS	2.0–2.5 L/hr	
NA	NA	AN69 0.82 ± 0.14, PS 0.9	NS	2.0–2.8 L/hr	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 L/hr	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 L/hr	
0.63 ± 0.25. Route of dilution NS		NA	0.5 g 12 hourly	1.5–1.8 L/hr	
NA	NA	0.65 ± 0.25	750 mg 8 hourly or 1.5 g 12 hourly	1.11–2.55 L/hr	Predilution
NA	NA	0.84 ± 0.16	400 mg daily	2 L/hr	Predilution
0.47 ± 0.27. Route of dilution NS		NA	NS	Mean ± SD 3.2 ± 0.9 L/hr	
NA	0.62	NA	250 mg 24 hourly or 500 mg 48 hourly	0.8–1.3 L/hr	
NA	NA	0.61	250 mg 24 hourly 500 mg 48 hourly	2–2.4 L/hr	Postdilution
NA	NA	0.73 ± 0.14	250 mg daily	Mean 2.2 L/hr	Predilution
0.79 ± 0.14	NA	NA	200 mg daily	Mean 1.2 L/hr	
NA	0.98 ± 0.06	NA	Initial 500 mg, then 250 mg daily	1.3 L/hr	
NA	NA	0.67	400 mg daily	0.54–1.26 L/hr	
NA	NA	0.63	400 mg daily	1.84–2.24 L/hr	
NA	NA	0.70 ± 0.13	300 mg12 hourly	3 L/hr	Predilution
0.89 ± 0.35.Route of dilution NS		NA	NS	Mean ± SD 27 ± 5 ml/kg/hr	
NA	NA	Mean ±SEM 0.5 ± 0.067	NS	Mean 1.91 L/hr	
0.71 ± 0.19	NA	NA	NS	Mean ± SD 32 ± 9 ml/kg/hr	
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 (Clcr <20 ml/min)	0.5–1 L/hr	
NA	NA	0.70 ± 0.10	450 mg 12 hourly	3 L/hr	Predilution
NS	NS	NA	NS	0.5–1.0 L/hr	
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 L/hr	
0.76 ± 0.11	0.57 ± 0.15	NA	500 mg 6 hourly or 1 g 12 hourly	6 L/hr	High- volume CVVH
NA	NA	NS	NS	NS	
0.13–0.17	NA	NA	NS	1–2 L/hr	
NA	NA	NS	800 mg on day 1; 400 mg on days 2 and 3 then 400 mg 48–72 hourly	0.96 L/hr	
NA	NA	NA	NS	NS	
NA	NA	NS	NS	NS	Postdilution
NA	NA	NS	150 mg 12 hourly does not provide effective peak levels	0.6–2.2 L/hr	Postdilution
NS	NS	NA	NI	Mean 1.2 L/hr	
NS	NS	0.62 ± 0.2	10 mg/kg 48 hourly	2 L/hr	
NA	NA	NA	NS	NS	
NA	NA	NS	Colistin methanesulfonate: 2–3 mg/kg 12 hourly	3 L/hr	Postdilution Data from a single patient
0.57	NA	NA	NS	2–2.5 L/hr	
0.84	NA	NA	NS	2 L/hr	
NA	0.77 ± 0.09	NA	600 mg at least 12 hourly	1.5–3.0 L/hr	
NA	0.69 ± 0.12	NA	600 mg at Least 12 hourly	1.5–3.0 L/hr	
PS: 0.16–0.20; AN69: 0.14–0.16		NA		1–6 L/hr	*In vitro* data

(*Continued*)

Table 5.—*Continued*

Drug (Reference)	Mode of CRRT (No Patients)	Residual Renal Function	Volume of Distribution	Non-CRRT Clearance (mL/min)	Membrane/Surface Area
Daptomycin (119)	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)					

AN69, acrylonitrile; CAVH, continuous arteriovenous hemofiltration; CAVHD, continuous arteriovenous hemodialysis; CAVHDF, continuous arteriovenous hemodiafiltration; Clcr, creatinine clearance; Clurea, urea clearance; CRRT, continuous renal replacement therapy; CT, cellulose triacetate; CVVH, continuous venovenous hemofiltration; CVVHD, continuous venovenous hemodialysis; CVVHDF, continuous venovenous hemodiafiltration; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; NA, not available; NI, not interpretable; NS, not specified; PA, polyamide; PAN, polyacrylonitrile; PMMA, polymethylmethacrylate; post, postdilution; pre, predilution; PS, polysulfone; pts, patients; S_c, sieving coefficient; S_d, saturation coefficient; U/O, urine output.

Values in parentheses indicate the No patients. Pharmacokinetic data are steady-state data unless otherwise stated.

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efficiency. As a result, simple addition of each component will lead to an overestimation of total clearance but the clinical relevance is unclear (32). Nevertheless, CVVHDF has been shown to provide greater clearance than predilution CVVH with equivalent effluent (ultrafiltrate plus dialysate) flow (33).

Pharmacokinetic Factors Influencing Initial Doses of Antibacterials

Volume of distribution should be the primary pharmacokinetic consideration when determining initial dose. Although both critical illness and acute renal failure may affect volume of distribution, CRRT itself generally has no effect. Although antibacterial volume of distribution would be expected to increase in the critically ill (34) and those with acute renal failure, this is only the case for certain agents. For example, available data suggest that the volume of distribution of ciprofloxacin and meropenem is not increased in critically ill patients, with or without acute renal failure, compared with healthy volunteers (26, 35–44). Although the volume of distribution of ceftriaxone appears to be increased by both critical illness and renal failure (45), in general, the volume of distribution of ceftazidime is predominantly affected by renal failure (46, 47). The volume of distribution of netilmicin is considerably higher in critically ill patients with renal failure than in healthy volunteers, and the volume of distribution of amikacin is higher in critically ill patients without renal failure than in healthy volunteers (48).

Pharmacokinetic Factors Influencing Maintenance Doses

Maintenance doses are determined by antibacterial clearance. This can be divided into non-CRRT clearance (renal clearance due to residual renal function plus nonrenal clearance) and CRRT clearance. Nonrenal clearance may be affected by critical illness, for example, because of hepatic dysfunction. It may also be increased in the presence of acute renal failure (49, 50). CRRT clearance is affected by PB, adsorption, and Gibbs-Donnan effect (51). The Gibbs-Donnan effect refers to the effect of retained anionic protein (such as albumin) on the blood side of the filter membrane. This leads to the retention of cationic drugs such as aminoglycosides and levofloxacin. The opposite is true for anionic drugs such as ceftazidime and cefotaxime (51). However, the clinical relevance of this effect is unclear (23, 29, 52).

Disease states, such as uremia, cirrhosis, nephrotic syndrome, epilepsy, hepatitis, pregnancy, and severe burns—which in the critically ill may occur concomitantly—have been shown to decrease PB 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 (51). 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 further increased by renal failure (45). As a result, clearance by CRRT is likely to be higher than would be expected from PB in healthy volunteers and this is confirmed by experimental data (53, 54).

In general, drugs with a large volume of distribution are poorly eliminated by CRRT because 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 (7). However, similar considerations apply to elimination by the kidneys in patients with normal renal function. Both ciprofloxacin and levofloxacin have V_d >1.5 L/kg yet renal clearance accounts for ≥70% of total clearance (55, 56). 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 volume of distribution is a fall in PB, elimination by CRRT (and kidneys) will be affected by an increase in free fraction of the drug. In general, drugs with a high volume of distribution (>1 L/kg) and high PB (>80%) are poorly eliminated by CRRT (57).

Besides convection and diffusion, a third potential mechanism for solute removal during CRRT is adsorption. This has been poorly studied to date. Limited *in vitro* data suggest that adsorption is both membrane and drug dependent (29, 52, 58). At clinically relevant concentrations, adsorption of levofloxacin and vancomycin is unlikely to be clinically significant (29, 58); however, a significant amount of amikacin binds irreversibly to sulfonated polyacrylonitrile membranes *in vitro* (52). The clinical importance of adsorption of antibacterials is currently unknown but worthy of investigation.

Table 5.—*Continued*

S_c (Pre)	S_c (Post)	S_d	Dose Recommended by Authors	Total Effluent Rate (Range, Unless Otherwise Specified)	Remarks
NA	NA	PS: 0.15 AN69: 0.05–0.13		1–6 L/hr	*In vitro* data

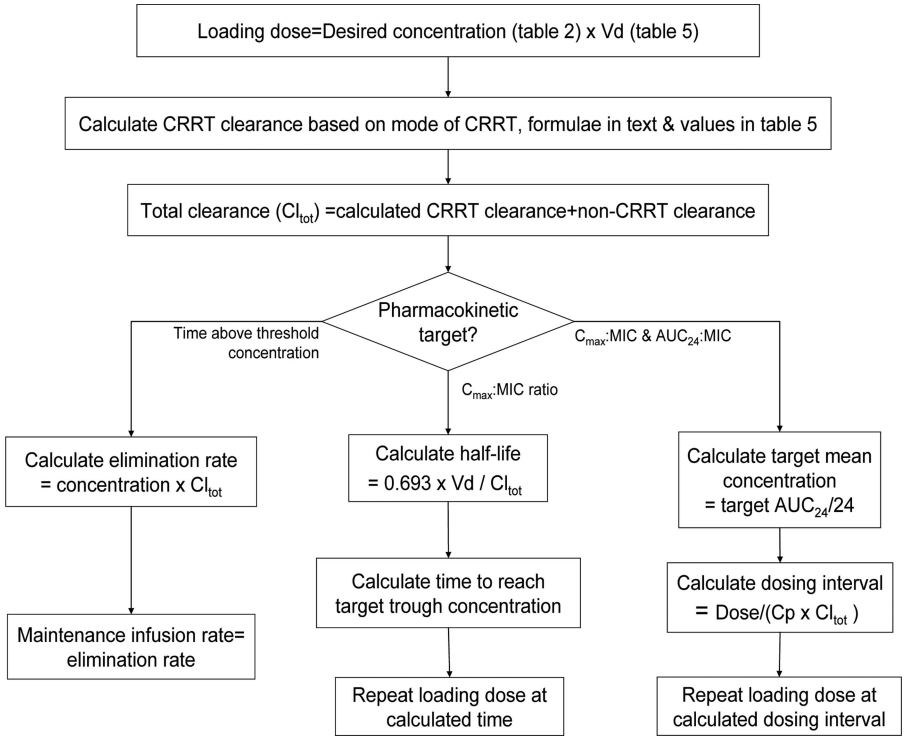

Figure 3. Calculation of intravenous antibacterial doses based on first principles. Noncontinuous renal replacement therapy (*CRRT*) clearance is the sum of nonrenal clearance plus residual renal clearance. Cl_{tot}, total clearance; C_{max}, maximum postdistribution plasma concentration; *MIC*, minimum inhibitory concentration; AUC_{24}, area under concentration-time curve over 24 hours; V_d, volume of distribution; *Cp*, target plasma concentration.

Critique of Currently Available Dosage Regimes

From the above, it can be seen that there are many factors that need to be taken into account when determining appropriate doses of antibacterials for critically ill patients receiving CRRT (Table 3). Although there are multiple sources of recommendations for antibacterial dosing in this group of patients, none of the patients take all of these factors into account. If those dose recommendations based on estimated glomerular filtration rate are used, the average daily effluent rate can be substituted for the glomerular filtration rate. Dosages based on the findings of individual studies may also not be appropriate unless the mode and dose of CRRT are identical to those in the study. Furthermore, it is difficult to follow dose recommendations from individual studies when the dose of CRRT within a study is variable (Table 5). Dosage recommendations for patients with chronic renal failure undergoing intermittent renal replacement therapy are not appropriate because of differences in dose and mode of renal replacement therapy as well as pharmacokinetic differences (59). Some currently proposed dosage regimes and their associated assumptions are listed in Table 4. Unfortunately, these assumptions may not be valid. For many antibacterials, assays are not widely available for clinical use, S_c is not invariably the same as the unbound fraction, and "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 (60) and the MIC for *Streptococcus pneumoniae* (61), the recommended dose of moxifloxacin may not achieve an optimal AUC:MIC >33.7 (62) in some countries, where the MIC is high but still below accepted break points. Furthermore, method 4 consistently overestimates daily dosing needs for drugs with low nonrenal clearance (63).

Although other recommendations on antibacterial dosing during CRRT are available (7, 59, 64), these recommendations are based on either continuous arteriovenous hemofiltration data or suboptimal ultrafiltration/dialysate flow rates (65–67).

Given the variability in mode and dosing of CRRT and in MIC in different intensive care units, we believe the most appropriate way to dose antibacterials may be to calculate an appropriate individualized dose from first principles. The initial dose is dependent on the volume of distribution. Maintenance doses are dependent on clearance. Both need to be adjusted according to the pharmacokinetic target associated with optimal kill-

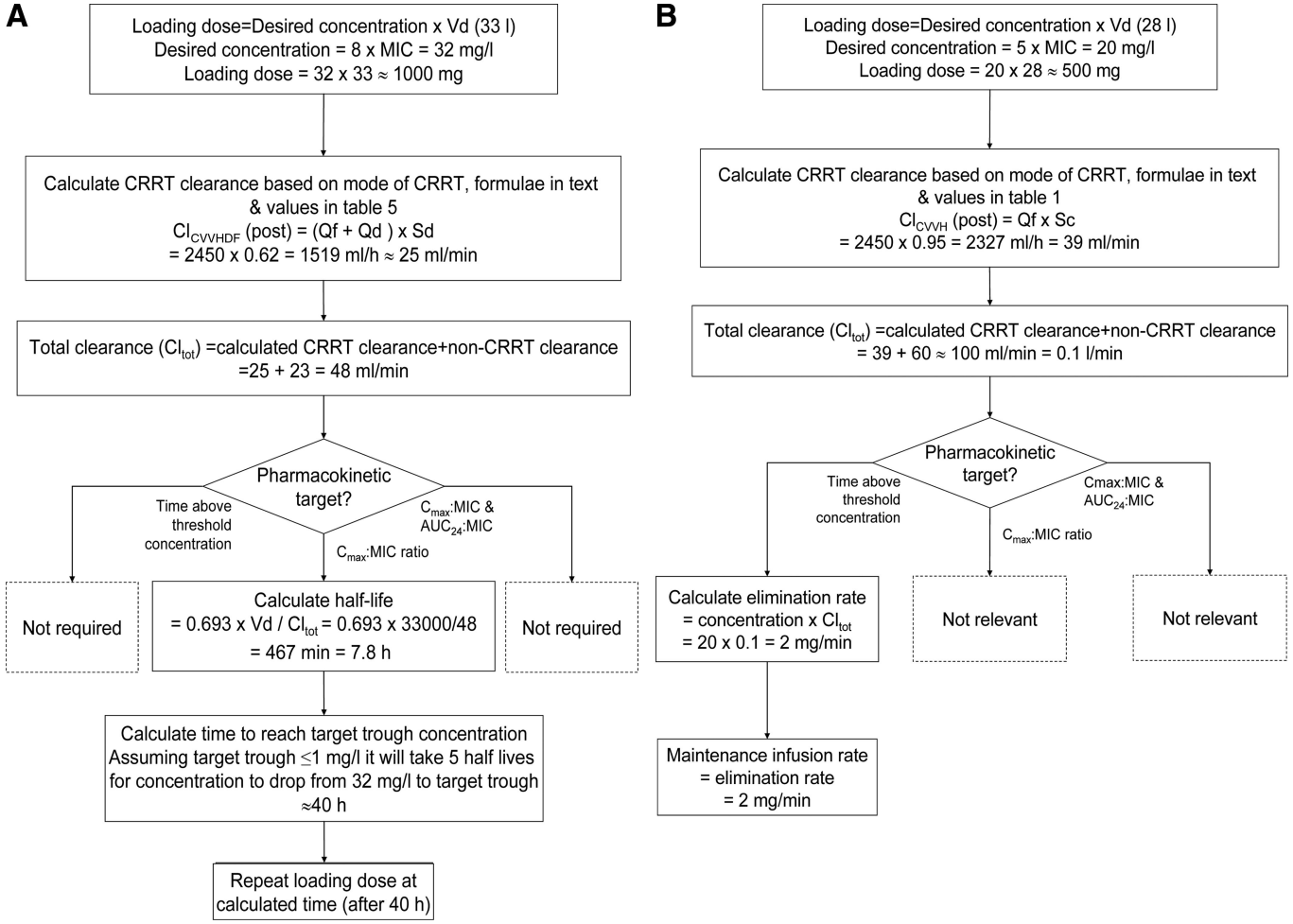

Figure 4. *A*, Calculation of amikacin dose for empirical non-enterobacteriaceae nosocomial sepsis for a 70-kg patient with anuric acute renal failure on continuous venovenous hemodiafiltration using an AN69 filter and with targeted total effluent of 35 mL·kg·hr. Note that figures are included for illustrative purposes. Dose prescribed should also take into account the risk of toxicity and may need to be reduced to comply with dose range approved by regulatory authorities. *B*, Calculation of dose of meropenem for empirical non-enterobacteriaceae/enterobacteriaceae/*Staphylococcus* nosocomial sepsis for a 70-kg patient with anuric acute renal failure on continuous venovenous hemofiltration (postdilution) using AN69 0.9 m^2 filter with a targeted ultrafiltration rate of 35 mL·kg·hr. 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 dose range approved by regulatory authorities. Cl_{tot}, total clearance; C_{max}, maximum postdistribution plasma concentration; MIC, minimum inhibitory concentration; AUC_{24}, area under concentration–time curve over 24 hours; *CRRT*, continuous renal replacement therapy; Q_f, ultrafiltrate flow rate; Q_d, dialysate flow rate; S_d, saturation coefficient; Cl_{CVVH}, clearance by continuous venovenous hemofiltration; V_d, volume of distribution; Cl_{CVVHDF}, clearance by continuous venovenous hemodiafiltration.

ing. Thus, appropriate dose calculation requires knowledge of pharmacokinetic target (Table 2) and the usual MIC of the suspected organism in your locality (if unavailable, the break point for the organism may be appropriate), published pharmacokinetic data (volume of distribution, non-CRRT clearance) on critically ill patients receiving CRRT (Table 5), the S_c or S_d of the relevant drug (Table 5), and the dose and mode of CRRT being used (Figs. 3 and 4). Several aspects of this recommendation require elaboration. First, for the sake of simplicity, the formula recommended for calculation of 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 of continuous infusions on outcome. If intermittent bolus doses are used, the appropriate maintenance dose can be calculated from:

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

and

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

where $k = \frac{CL}{V_d}$, T = dosing interval (mins) and Cth= target threshold concentration.

Third, for patients with residual renal function, total clearance needs to be adjusted for renal clearance. In this context, it is important to understand that adjustment for renal clearance based on creatinine clearance assumes that drugs undergo glomerular filtration only and therefore will result in underdosing for drugs with important tubular secretion or overdosing for drugs with tubular resorption (8). Dosing should also take into account the effect of other organ failure (e.g., hepatic) on non-CRRT clearance. Fourth, when drug 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 val-

ues. Fifth, 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 understand 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 intrapatient 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 five times MIC) and the MIC. It is important that these doses are not prescribed unthinkingly, but that the benefits of optimal killing are balanced against the risks of toxicity and that the possibility of using another agent with a more favorable risk:benefit ratio is considered. When no suitable alternative exists, it may be prudent to restrict doses to the doses approved by regulatory authorities. However, when considering the risk of toxicity it is important to understand that, although toxicity is associated with drug concentrations, the relationship is not simple and is dependent on a large number of factors that vary from agent to agent (68–72). Furthermore, underdosing is an important factor in development of antibacterial resistance (4).

It is also important to understand that all the dosing recommendations provided, both old and new, provide only estimated doses and when possible doses should be further adjusted according to measured blood concentrations. However, blood concentrations alone are unlikely to be sufficient in guiding dosing. First, they cannot provide guidance on initial doses and second, there is often a significant delay between blood sampling and delivery of results.

In theory, when suitable assays are available, it is possible to calculate drug clearance by CRRT from blood concentrations and from the volume and drug concentration in a timed effluent collection. This requires either frequent blood sampling or selection of a period during which drug concentrations in blood are unlikely to be changing rapidly and careful timing of the effluent collection. Furthermore, as with all methods based on drug assays, there may be a significant delay in obtaining results unless the appropriate laboratory provides a rapid service at all hours.

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 (73). In these cases, our proposed method of calculating an appropriate dose is not useful.

Summary and Conclusions

Optimal bacterial killing by antibacterials is dependent on achieving pharmacodynamic targets associated with maximal killing of bacteria. To achieve these targets, it is important to be aware of the changes in PB, volume of distribution, and nonrenal clearance associated with the combination of critical illness and renal failure as well as the determinants of clearance by CRRT. When considering clearance by CRRT, it is also vital to understand that not only are mode (pre- or postdilution and CVVH, CVVHDF, or CVVHD) and dose of CRRT major determinants of clearance, but they may also vary considerably between intensive care units and patients and within patients from day to day. Furthermore, there may be a difference between prescribed and administered doses of CRRT due to interruptions in treatment. Thus, the situation is very different from the more homogeneous situation of chronic renal failure and intermittent dialysis and necessitates a different approach to dosing. We believe that the most appropriate method of dosing is to individualize dosing taking into account the above factors and balancing the benefits of optimal killing against the risk of drug toxicity.

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