

## A systematic review of antibiotic dosing regimens for septic patients receiving continuous renal replacement therapy: do current studies supply sufficient data?

A. M. M. Y. Li<sup>1\*</sup>, C. D. Gomersall<sup>1</sup>, G. Choi<sup>1</sup>, Q. Tian<sup>1</sup>, G. M. Joynt<sup>1</sup> and J. Lipman<sup>2</sup>

<sup>1</sup>Department of Anaesthesia & Intensive Care, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong; <sup>2</sup>Burns Trauma Critical Care Research Centre, University of Queensland, Herston QLD 4029, Australia

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**Background:** Drug dosing for septic patients with acute renal failure receiving continuous renal replacement therapy (CRRT) is complicated, and failure to correctly dose may result in either drug toxicity or treatment failure and development of antibiotic resistance. The aim of this study was to establish an ideal dataset that needs to be reported when presenting pharmacokinetic data for these patients and review current literature for completeness of this dataset.

**Methods:** An ideal dataset was established of the parameters that should be reported when calculating a drug dosing regimen from first principles. A Medline search was performed of relevant literature producing 64 citations from which completeness of the specified criteria was examined.

**Results:** None of the studies analysed presented the full dataset that we established as necessary. Of concern, basic pharmacokinetic parameters such as volume of distribution ( $V_d$ ) and clearance (CL) were specified in only 79% and 81% of studies, respectively.

**Conclusions:** A large proportion of current studies do not report key information necessary to devise a rational dosing regimen for patients with acute renal failure receiving CRRT, and we hope this dataset will be a useful guide when reporting future pharmacokinetic data.

Keywords: antibiotics, drug dosing, pharmacokinetics, renal replacement therapy, sepsis

### Introduction

Sepsis and acute renal failure (ARF) are two pathological entities that commonly co-exist in patients admitted to intensive care.<sup>1,2</sup> Early, appropriate antibiotic therapy and source control while enhancing cellular recovery and controlling metabolic complications associated with uraemia remain the most important aspects of clinical treatment.<sup>3–7</sup>

However, antibiotic dosing in septic patients with ARF can be complicated and may result in either underdosing, causing treatment failure and antibiotic resistance, or overdosing resulting in drug toxicity.<sup>8</sup> This is further compounded by the use of renal replacement therapy (RRT) to maintain homeostasis until renal function has sufficiently recovered, which can result in significant non-renal clearance of antibiotic.<sup>9</sup>

Since the late 1970s the use of continuous renal replacement therapy (CRRT) has become established in many intensive care

units (ICUs) as the preferred modality of RRT. CRRT avoids rapid fluid and electrolyte shifts in haemodynamically unstable patients and gives better control of patient fluid balance than traditional thrice-weekly intermittent haemodialysis (IHD). CRRT is usually performed through a venous catheter situated in a large (usually a femoral or internal jugular) vein, either as continuous veno-venous haemofiltration (CVVH), haemodialysis (CVVHD) or a combination of the two: haemodiafiltration (CVVHDF).

CVVH uses a predominantly hydrostatic pressure gradient to pump solute across a filter membrane to achieve clearance. Replacement fluid can be added to the circuit either before blood reaches the membrane (pre-dilution) or after passage over the filter membrane (post-dilution). In contrast, CVVHD uses diffusion across a membrane to effect clearance of solute. This is achieved by generating a continuous concentration gradient using counter-current flow of plasma and dialysate fluid,

\*Corresponding author. E-mail: alex\_li@mac.com

between which equilibration occurs. CVVHDF uses a combination of the two above techniques, convection and diffusion to clear solute.

In order to devise a rational drug dosing regimen it is necessary to know the volume of distribution ( $V_d$ ) and the clearance (CL) of the drug concerned. In the case of patients with ARF being treated with CRRT, clearance will depend on a combination of CRRT clearance, residual renal function and non-renal clearance. Both the volume of distribution and the non-renal clearance may be changed by ARF and critical illness.<sup>10–14</sup> The problem is further exacerbated by considerable variability in the mode and dose of CRRT. Thus, to be useful to clinicians, studies of antibiotic pharmacokinetics in critically ill patients with ARF should report several parameters in addition to the standard pharmacokinetic dataset. Without these parameters, interpretation of studies and their use in deriving a dosing regimen is limited.

The aim of this review therefore was to: (i) establish the ideal dataset that needs to be presented to allow for adequate antibiotic dosage regimen calculation on CRRT; (ii) examine recent publications on antibiotic dosing in patients with ARF receiving CRRT and to establish whether this dataset is complete; and (iii) examine whether sufficient detail on patient case-mix was given to assess applicability of the data to other critically ill patients receiving CRRT for ARF.

## Methods

### Establishing the ideal dataset required

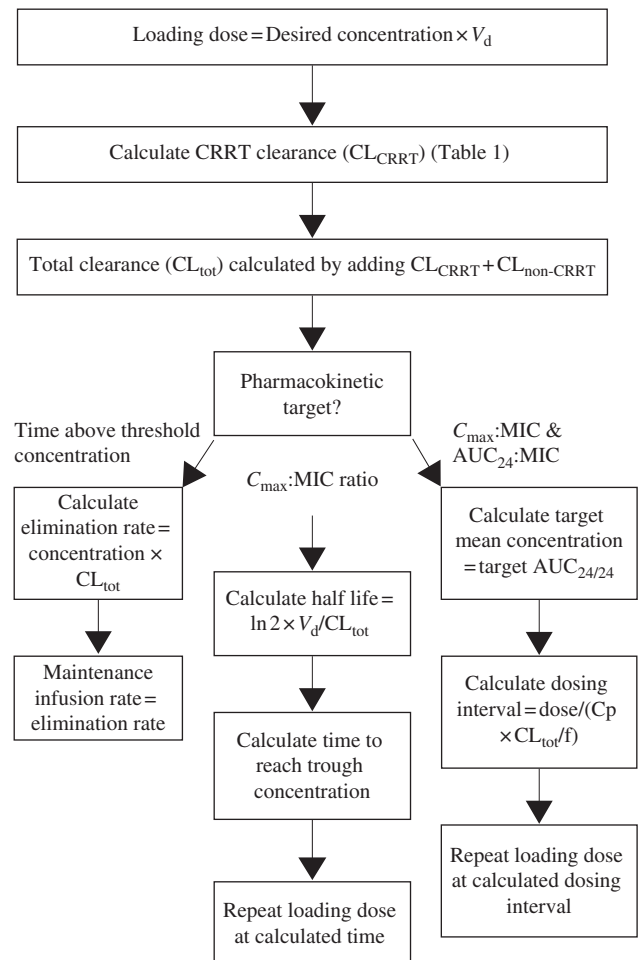
A drug dosing regimen can be calculated from first principles:  $V_d$  will determine initial or loading dose and total clearance ( $CL_{tot}$ ) will dictate dosing interval.  $CL_{tot}$  is determined by both CRRT ( $CL_{CRRT}$ ) and non-CRRT ( $CL_{non-CRRT}$ ) clearance (mainly residual renal and hepatic clearance). Thus, depending on whether antibiotic kill characteristics are time or concentration dependent, a specific serum concentration–time profile can be targeted (Figure 1).

The mode and dose of CRRT in critically ill patients with ARF is not only highly variable but can have significant effects on  $CL_{CRRT}$ , and therefore specific data need to be quoted. Table 1 shows equations for calculating CRRT clearance depending on the modality of CRRT used. Passage of drug across a filter membrane is essentially independent of drug molecular weight as the pore size of modern membranes vastly exceeds the size of most commonly used antimicrobials. However, protein binding, membrane type, charge and surface area may play a significant role in limiting drug passage across the haemofilter. This can be expressed, depending on whether CVVH or CVVHD is used, as either a sieving coefficient ( $S_c$ ) or a saturation coefficient ( $S_d$ ), calculated as:

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

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

When using CVVH, the method of dilution needs to be specified as plasma entering the haemofilter in predilution mode will be diluted by replacement fluid, and a correction factor (CF) needs to be used to calculate clearance ( $CF = Q_b / (Q_b + Q_{rep})$ ) (Table 1). This would require further mention of blood flow rates ( $Q_b$ ) and fluid



**Figure 1.** Calculation of antibacterial doses based on first principles: non-CRRT clearance is the sum of non-renal clearance plus residual renal clearance.

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

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

$CL_{CVVH} \text{ (post)}$ , clearance from continuous veno-venous haemofiltration using post filter haemodilution;  $Q_f$ , ultrafiltrate rate;  $S_c$ , sieving coefficient;  $CL_{CVVH} \text{ (pre)}$ , clearance from continuous veno-venous haemofiltration using pre-filter haemodilution;  $Q_b$ , blood flow rate;  $Q_{rep}$ , predilution replacement rate;  $CL_{CVVHD}$ , dialysate flow rate;  $S_d$ , saturation coefficient;  $CL_{CVVHDF}$ , clearance from continuous veno-venous haemodiafiltration.

replacement rates ( $Q_{rep}$ ) in addition to basic CVVH data such as  $S_c$  and ultrafiltrate rate ( $Q_f$ ). Non-CRRT clearance is predominantly determined by residual renal and hepatic clearance, which should therefore be mentioned in some form. Finally, to assess whether the derived dataset is applicable to the patient population one wants to

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dose, a comparison of patient demographics such as age, weight and severity of illness would be helpful.

Based on the principles discussed above, ideal (Figure 2) and minimum datasets were determined by three of the authors. Disagreements were resolved by discussion. The minimum dataset consisted of: antibiotic assayed, dose recommendation, patient age, weight, markers of residual renal function and hepatic impairment,  $V_d$ , clearance (total, CRRT and non-CRRT) and (depending on modality of CRRT used), method of dilution, ultrafiltrate, blood and dialysate flow rates.

### Literature review

We searched the Medline database from January 1986 through to February 2008 for literature with the medical subject headings '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'. All searches were limited to studies of human subjects and antimicrobials commonly used in intensive care. The searches produced a total of 64 citations, 60 related to antibacterials<sup>15–73</sup> and four related to antifungals<sup>89–92</sup> (see Table S1; available as Supplementary data at JAC Online <http://jac.oxfordjournals.org/>).

Three investigators reviewed potentially relevant papers for the specified data and any disagreement was resolved by discussion.

## Results

The percentage of studies providing the ideal dataset we specified is shown in Figure 3. Of note, none of the studies included the full set of parameters; 29% of studies provided the minimum dataset.

### Drug data

All studies specified the antibiotic assayed and 7% of studies specified a target concentration in terms of MIC. Dose recommendation or modification was suggested in 73% of studies.

### Patient demographics

All studies specified the number of patients receiving antibiotics and CRRT. Age and patient weight were given in 99% and 69%

Drug data					
Antibiotic assayed		Specified target concentration		Dose recommendation	

Patient demographics					
Age	Weight	Severity of illness	Number of patients in study	Residual renal function	Hepatic function

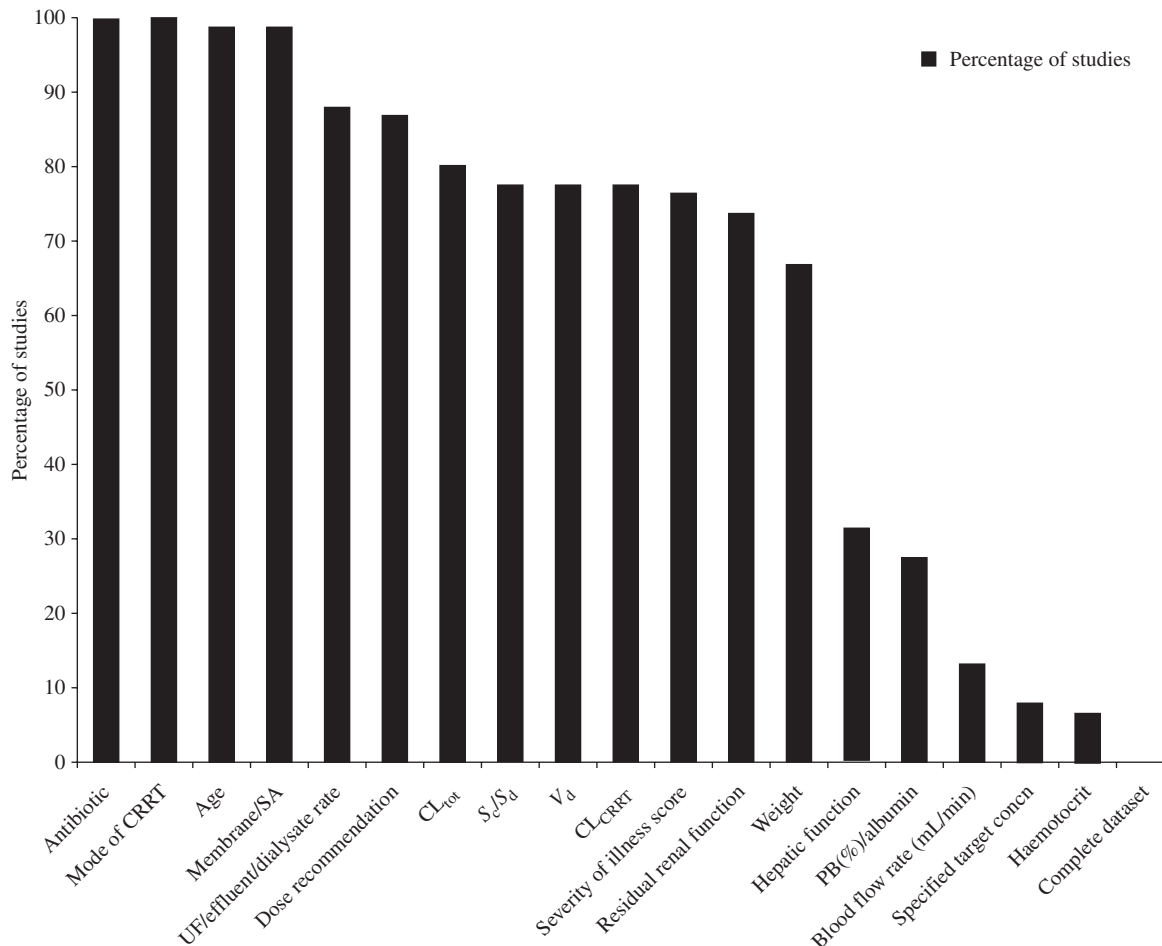
Basic pharmacokinetics		
Volume of distribution ( $V_d$ )	Total, CRRT and non-CRRT clearance	Protein binding/serum albumin

CRRT clearance			
Membrane type/surface area			
CVVH		CVVHD	CVVHDF
Pre-dilution	Post-dilution		
$S_c$	$S_c$	$S_d$	$S_c/S_d$
Ultrafiltration rate ( $Q_f$ )	Ultrafiltration rate ( $Q_f$ )	Dialysate rate ( $Q_d$ )	Ultrafiltration rate ( $Q_f$ ) and Dialysate rate ( $Q_d$ ) or Effluent rate ( $Q_f + Q_d$ )
Blood flow ( $Q_d$ )			
Haematocrit (HCT)			
Predilution replacement rate ( $Q_{rep}$ )			

**Figure 2.** Pharmacokinetic parameters required for antibiotic dosage modification in patients receiving CRRT.

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**Figure 3.** Percentage of studies specifying the required parameters for pharmacokinetic analysis. CRRT, continuous renal replacement therapy; SA, surface area; CL<sub>tot</sub>, total clearance; S<sub>c</sub>/S<sub>d</sub>, sieving/saturation coefficient; V<sub>d</sub>, volume of distribution; CL<sub>CRRT</sub>, CRRT clearance; PB, protein binding. Note effluent/dialysate rate includes ultrafiltrate (UF) rate where CVVH used.

of studies, respectively. Severity of patient's illness was specified in 80% of studies. Some measure of residual renal function was specified in 75% of studies, and a note of hepatic impairment or function, either qualitative or quantitative, was noted in 33% of studies.

### Basic pharmacokinetics

V<sub>d</sub> and CL<sub>tot</sub> were specified in 79% and 81% of studies, respectively. Protein binding or serum albumin was mentioned in 27% of studies.

### CRRT clearance

The most popular method of CRRT was CVVH, which accounted for 41% of studies. CVVHD and CVVHDF were used in 16% and 24% of studies respectively. Other modalities of CRRT included continuous arterio-venous haemofiltration (CAVH; 4%), continuous arterio-venous haemodialysis (CAVHD; 12%) and high-volume haemofiltration (HVHF; 1.3%). A combination of two of the above techniques was used in the remaining CRRT studies.

### CVVH

Pre- or post-dilution mode was specified in 58% of studies. S<sub>c</sub> was calculated in 63% of studies. The ultrafiltration rate was noted in 91% of studies. Where predilution was used, specification of blood flow rate (Q<sub>d</sub>) and haematocrit (HCT) (to calculate plasma flow rate) was mentioned in 80% and 6%, respectively (Figure 4).

### CVVHD

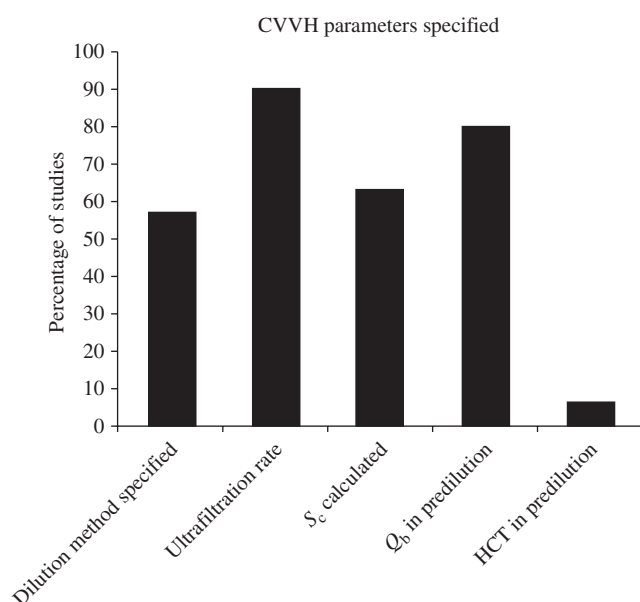
Dialysate rate and S<sub>d</sub> were specified in 67% and 42% of studies, respectively.

### CVVHDF

S<sub>c</sub>/S<sub>d</sub> and effluent rate (Q<sub>f</sub> + Q<sub>d</sub>) were specified in 67% and 89% of studies.

## Discussion

Our systematic review of the literature indicates that a large proportion of studies of antibiotic dosing in critically ill patients



**Figure 4.** Percentage of studies with necessary dataset to calculate clearance with CVVH.  $S_c$ , sieving coefficient;  $Q_b$ , blood flow rate; HCT, haematocrit.

receiving CRRT do not report key information necessary to devise a rational dosing regimen or to determine the applicability of the findings to the reader's patients. In fact, none of the studies analysed specified the full dataset.

There are certain basic pharmacokinetic parameters such as  $V_d$  and  $CL_{tot}$  that are fundamental requirements for all drug dosing. However, these were only specified in 79% and 81% of studies, respectively.

The mode and dose of CRRT are highly variable, but are important determinants for antibiotics normally cleared by the kidneys. It is therefore necessary to estimate CRRT clearance in each individual or, at the very least, know whether the mode and dose of CRRT used in a study approximates to the mode and dose being given to the patient. A small but significant proportion of studies omitted even basic information such as ultrafiltrate/dialysate rate (Figure 3).

CVVH was the most common modality used in the studies analysed, but only 58% of studies specified the method of replacing ultrafiltrate (Figure 4). Given the disparity that can arise in drug clearance between pre- and post-dilution CVVH, specification of pre-dilution where used, with calculation of an appropriate correction factor using blood flow rate ( $Q_b$ ) and replacement fluid rate ( $Q_{rep}$ ) is essential. One can argue that in most patients  $Q_{rep}$  will only vary by a small fraction of the blood flow rate ( $Q_b$ ) and therefore changes will probably not significantly affect overall CRRT clearance. Similarly, using haematocrit to estimate plasma flow rate as opposed to blood flow rate (as drug is essentially cleared from plasma), should likewise not significantly impact on overall clearance provided consistency exists between studies. However, both these parameters are easily measured and should therefore be included for study accuracy.

It is important to know  $S_c$  or  $S_d$  if one is to estimate drug clearance in an individual patient (Figure 2). If these data are lacking (1–protein binding) can be used as a surrogate<sup>74</sup> as protein binding is the principal determinant of  $S_c$  and  $S_d$ . Only 78% of studies gave  $S_c$  or  $S_d$ . Of those that did not, none measured protein binding.

The importance of specifying all these parameters is illustrated by two studies of meropenem pharmacokinetics during CVVH.<sup>16,27</sup> Patients were comparable demographically (age, weight and severity of illness). However, the use of different membranes (polyacrylonitrile compared with polysulfone) may have resulted in different  $S_c$  values ( $0.63 \pm 0.252$  compared with  $1.09 \pm 0.10$ ). In combination with differing ultrafiltrate rates (25–30 mL/min compared with  $45.8 \pm 6.2$  mL/min) this resulted in vastly different CRRT clearances between the two studies (17.2 mL/min compared with  $49.7 \pm 8.3$  mL/min), and consequently very different dose recommendations for similar patients (500 mg twice daily compared with 1 g three times a day of meropenem).

Non-CRRT clearance may make a major contribution to total drug clearance and can be difficult to quantitatively assess. The two main routes of drug elimination are renal and hepatic. Only 74% of studies qualified renal excretion to any degree, and the majority only qualitatively. Hepatic clearance is much more difficult to assess, but we believe some mention of hepatic impairment, if it exists, should be specified. This may be qualitative in specifying a degree of liver impairment (for example the presence or absence of cirrhosis) or semi-quantitative such as serum bilirubin or a measure of hepatic perfusion with indocyanine green clearance. 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. Consequently, hepatic clearance in the presence of renal failure can become the predominant modality of drug elimination in certain cases.<sup>15</sup> For example, non-renal (hepatic) clearance of meropenem has been shown to increase from 20% of total elimination to >50% in patients with a creatinine clearance rate of <30 mL/min.<sup>75</sup>

Most studies suggested a dose regimen based on study data. Where one was not advocated, levels and further studies were suggested in the majority. Optimal bacterial killing is related to pharmacokinetic targets, which are in turn related to MIC. Thus to determine whether these dose regimens and modifications are appropriate it is necessary to know what pharmacokinetic endpoint was targeted and that endpoint should be referenced to MIC. However, this only occurred in 8% of studies.

We believe patient demographic data should be reported to allow the reader to judge whether the findings can be applied to his/her patient. Patient age was included in the dataset as it has significant effects on native renal and hepatic clearance causing *in vivo* drug clearance variations of 20%–40%,<sup>76</sup> as well as effecting changes in total body water, plasma protein binding and  $V_d$ .<sup>77</sup> Similarly, weight variation can have significant effects on volume of distribution, and some studies specified  $V_d$  only in absolute volume, which needs to be corrected for patient weight for comparison. In addition, studies of the optimal intensity of CRRT reference the CRRT dose to weight.<sup>78–80</sup> Finally we looked for an indication of severity of illness for comparison between ICU populations. Critical illness may have significant pharmacokinetic effects *per se*, and clearance alterations and increases in the  $V_d$  of aminoglycoside,  $\beta$ -lactam and carbapenem antibiotics in critically ill septic patients have been reported.<sup>81–86</sup> Although unproved, this seems unlikely to be an all-or-nothing phenomenon but is related to the severity of illness.

Our discussion has focused on the data required for dose calculation from first principles. While we believe this is the ideal method of prescription, many clinicians will choose to use dose



**Table 2.** Currently available methods of estimating antibacterial dose in patients receiving CRRT from literature

Method	Study	Mode of CRRT	Calculation of dose
1	Golper <i>et al.</i> <sup>76</sup>	CVVH	$D = C_{ss} \times UBF \times UFR \times I$
2	Bugge <i>et al.</i> <sup>89</sup>	CVVHDF	$D = D_N \times (P_x + (1 - P_x)) \frac{CL_{CRt}}{CL_{CRn}}$
3	Schetz <i>et al.</i> <sup>90</sup>	CVVH	$D = D_N \left( \frac{CL_{NR} + (UFR \times S_c)}{CL_N} \right)$
4	Schetz <i>et al.</i> <sup>90</sup>	all modes	$D = \frac{D_{anuria}}{1 - \left( \frac{CL_{EC}}{CL_{EC} + CL_{NR} + CL_R} \right)}$

$C_{ss}$ , measured blood concentration at steady state;  $CL_{ANUR}$ , drug clearance in anuric patient;  $CL_{CRn}$ , normal creatinine clearance;  $CL_{CRt}$ , sum of renal and extracorporeal 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.

adjustment equations (Table 2). As can be seen from Table 2 the dose adjustment equations require many of the parameters discussed above such as  $CL_{CRRT}$  and  $CL_{non-CRRT}$ ,  $S_c$  and CRRT dose.

A third alternative is a 'best guess' technique whereby one could identify studies using the antibiotic in question which have similar patient demographics, modality and dose of CRRT, and then use the advocated dosing regimen of these studies if patients and practice are sufficiently similar to that used in the prescriber's unit. Again, this would require specification of most of the parameters in our dataset.

## Conclusions

We have presented a set of criteria we think necessary to calculate appropriate doses of antibiotics in septic patients receiving CRRT, from first principles. None of the studies of pharmacokinetic data examined presented the full range that we specified. Clearly some parameters are of greater importance in calculating clearance than others. As non-renal indications for haemofiltration and haemodialysis continue to expand with the concept of blood purification, the use of these parameters in calculating CRRT drug clearance in patients with both impaired and normal hepato-renal function will increasingly become an important issue. We hope our dataset will be a useful guide when deciding which parameters are worthy of inclusion.

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## Transparency declarations

None to declare.

## Supplementary data

Table S1 is available as Supplementary data at JAC Online (<http://jac.oxfordjournals.org/>).

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