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Title: To increase or decrease dosage of antimicrobials in septic patients during continuous renal replacement therapy: the eternal doubt.

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Abstract: Critical illness, acute renal failure and continuous renal replacement therapy (CRRT) are associated with changes in pharmacokinetics. Initial antibiotic dose should be based on published volume of distribution and generally be at least the standard dose, as volume of distribution is usually unchanged or increased. Subsequent doses should be based on total clearance. Total clearance varies with the CRRT clearance which mainly depends on effluent flow rate, sieving coefficient/saturation coefficient. As antibiotic clearance by healthy kidneys is usually higher than clearance by CRRT, except for colistin, subsequent doses should generally be lower than given to patients without renal dysfunction. In the future therapeutic drug monitoring, together with sophisticated pharmacokinetic models taking into account the pharmacokinetic variability, may enable more appropriate individualized dosing.

Conflict of interest statement

The Department of Anaesthesia & Intensive Care, The Chinese University of Hong Kong has received funding for educational activities from Astellas and Pfizer.

Professor Lipman has received speakers fees from Bayer and Astra Zeneca, research funding from Astra Zeneca and serves as a consultant to Astra Zeneca and as a member of an advisory board for Bayer.

***Detailed Response to Reviewers**

Section on dosing of colistin and daptomycin. This section would greatly benefit from a final sentence for each of the two mentioned drugs summarizing the authors' opinions on how to appropriately manage dosage in this setting.
The following statements have been added:
In view of the uncertainty regarding colistin pharmacokinetics combined uncertainty regarding the optimal pharmacokinetic / pharmacodynamic target we do not recommend calculating a dose but suggest giving at least the recommended dose for patients with normal renal function (3 million units 8 hourly) for patients receiving CRRT with effluent rates of 2.1– 3.4L/h. Other authors have suggested a more aggressive regime of a loading dose of 9 million units, followed by a maintenance dose of up to 4.5 million units 8 hourly, without the risk of toxicity[27].

In view of its kill and toxicity characteristics, daptomycin should be dosed using an extended interval dosing regime. Using the information and formulae above, the method detailed in our previous publication [1], a minimum dose and dosing interval can be calculated. For Staphylococcal aureus blood stream infection with MIC of 0.5 mg/L for a 70kg patient with anuria on CVVHD using a Polysulfone filter and with targeted total effluent of 35 ml/kg/hour, a loading dose of 800mg daptomycin with subsequent maintenance dosing interval of 34 hours should achieve a Cmax/MIC of 100 and minimise the risk of adverse effects. (Figure 1). However it is important to appreciate this calculated dose may need to be reduced in order to comply with dose range approved by regulatory authorities. It is of interest to note that healthy individuals receiving daptomycin at doses up to 12mg/kg daily for 14 days did not develop electrocardiographic or electrophysiological evidence of muscle or nerve toxicity[33].

A ref. supporting the statement about Cmax/MIC ratio of daptomycin against Staph is needed.
This had been added

Table 1 should be removed as it's not essential for the purposes of the review
The table has been removed

Table 2: the term hour must be always reported as "h" throughout the table. Use piperacillin/tazobactam instead of Tazocin. Add footnotes with the meaning of the abbreviations
The table has been amended

Conclusions should also decribe briefly the authors' opinion on future directions.
The following statement has been added:
Future directions should include the conduct of large scale studies of patients receiving CRRT with creation of pharmacokinetic models which can be used to generate recommendations on dosing changes in response to the results of therapeutic drug monitoring. This should be accompanied by development of therapeutic drug monitoring with a rapid turn-around time to allow prompt adjustment.

Minor comments.
The acronym MIC should be used throughout the text after that it has been exploded the first time
Manuscript amended

Section on Pharmacokinetic change due to renal failure. Use changes and not change in the subheading.
Linezolid must be considered as a lipophilic drug and not as an hydrophilic one.
Manuscript amended

Section on Pharmacokinetic change due to variability of CRRT. Use changes and not change in the subheading.
Manuscript amended

Section on Prescription of initial dose and subsequnt dose. Consider modifying subheadin as Prescription of initial loading dose and subsequent maintenance doses
Manuscript amended

There are some typo errors throughout the text. Please check carefully (i.e. doses and not dose in the highlights; demonstrates and not demonstrate, antibiotics and not antiotics in Ref. #21; pharmacokinetics and not pharmakinetics, pharmacodynamics and not pharmacodynmics, in the criticalli ill and not in critically ill in Ref. #23; demonstrates and not demonstrate, individualized and not individualised in Ref. #32))
Typos corrected

***Highlights (for review)**

Highlights

- Pharmacokinetics vary markedly in critically ill patients receiving CRRT.
- Prescribe initial dose of antibiotics based on volume of distribution.
- Prescribe subsequent doses based on CRRT and non CRRT clearance.
- Unlike other antibiotics, clearance of colistin by CRRT is greater than by healthy kidney.
- Therapeutic drug monitoring is useful to further individualize drug dosing.

To increase or decrease dosage of antimicrobials in septic patients during continuous renal replacement therapy: the eternal doubt.

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Abstract

Critical illness, acute renal failure and continuous renal replacement therapy (CRRT) are associated with changes in pharmacokinetics. Initial antibiotic dose should be based on published volume of distribution and generally be at least the standard dose, as volume of distribution is usually unchanged or increased. Subsequent doses should be based on total clearance. Total clearance varies with the CRRT clearance which mainly depends on effluent flow rate, sieving coefficient/saturation coefficient. As antibiotic clearance by healthy kidneys is usually higher than clearance by CRRT, except for colistin, subsequent doses should generally be lower than given to patients without renal dysfunction. In the future therapeutic drug monitoring, together with sophisticated pharmacokinetic models taking into account the pharmacokinetic variability, may enable more appropriate individualized dosing.

Highlights

- Pharmacokinetics vary markedly in critically ill patients receiving CRRT.
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Introduction

Optimal dosing of antibiotics is difficult because doses cannot be titrated to effect. Instead dosing should be designed to achieve pharmacokinetic targets associated with optimal killing. The pharmacokinetic parameters vary with the class of antibiotic and the target values depend on the organism and the susceptibility of the organism, as reflected by the minimum inhibitory concentration (MIC) ~~(table 1)~~. Given that the targets are pharmacokinetic parameters, it is self-evident that appropriate antibiotic dosing in patients receiving continuous renal replacement therapies (CRRT) requires knowledge of the pharmacokinetic changes that occur in these patients as well as the clearances obtained by the specific CRRT used.

Continuous renal replacement therapies are modes of therapy which are applied almost exclusively in Intensive Care Units. As a result drug pharmacokinetics in patients receiving CRRT are affected by changes due to critical illness, acute renal failure and the therapy. These issues have previously been reviewed by us [1] and will be dealt with only briefly here.

Pharmacokinetic changes due to renal failure

Changes in drug pharmacokinetics associated with critical illness and acute renal failure include increases in volume of distribution for some drugs (eg colistin [2], daptomycin [3,4], amikacin [5]) but not all. In general the volume of distribution of hydrophilic antibiotics (e.g. aminoglycosides, beta lactams, glycopeptides~~, linezolid~~) increases more than lipophilic antibiotics (e.g. macrolides, linezolid and fluoroquinolones) which already have a large volume of distribution [6]. Furthermore there may be

increases in non-renal clearance [7] and some residual renal function despite the presence of acute renal failure and CRRT.

There are three main modalities of continuous renal replacement therapy (CRRT): continuous veno-venous haemodialysis (CVVHD), continuous veno-venous haemofiltration (CVVH) and continuous veno-venous haemodiafiltration (CVVHDF). Clearance of solutes by these modalities is dependent on a number of factors as described in the following equations [1]:

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

$$Cl_{CVVH(pre)} = Q_f \times S_c \times \frac{Q_b}{Q_b + Q_{rep}}$$

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

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

Where $Cl_{CVVH\ (post)}$= clearance by continuous veno-venous haemofiltration with replacement fluid infused post-filter, $Cl_{CVVH\ (pre)}$= clearance by continuous veno-venous haemofiltration with replacement fluid infused pre-filter, Cl_{CVVHD}= clearance by continuous veno-venous haemodialysis, Cl_{CVVHDF}= clearance by continuous veno-venous haemodiafiltration, Q_b=blood flow rate, Q_d= dialysate flow rate, Q_f= ultrafiltrate flow rate, Q_{rep}=replacement fluid flow rate, S_c= sieving coefficient, S_d= saturation coefficient

From these equations it can be seen that the main determinants of elimination by CRRT are sieving or saturation coefficient and effluent flow rate (ultrafiltration rate, dialysate flow rate or the two combined). Blood flow rate plays a relatively minor role. The sieving coefficient and the saturation coefficient describe the ratio of solute concentration in the blood to the solute concentration in ultrafiltrate (sieving coefficient) or the dialysate (saturation coefficient). Drugs are often bound to plasma proteins which are large molecules that cannot cross the dialysis or haemofiltration membrane and therefore only unbound drug (free drug) is dialyzed or filtered. As a result sieving coefficient and saturation coefficient are related to the unbound fraction. Acute phase changes in plasma protein concentrations are common in critical illness, affecting the sieving and saturation coefficients [8]. Thus, in critically ill patients these coefficients may not reflect the unbound fractions normally measured in healthy volunteers. Furthermore there may be significant patient to patient variation in these coefficients (table 1~~2~~). Different filter materials may also be associated with different coefficients [1].

Pharmacokinetic change~~s~~ due to variability of CRRT

The issue is further complicated by the fact that continuous renal replacement therapy is not a single modality applied in a uniform way. Instead considerable variation in effluent rate between patients and between Intensive Care Units is common, filter or dialyzer material may vary and replacement fluid may be infused pre or post filter. Furthermore it is frequently not continuous but is interrupted for technical reasons and to transport the patient out of the Intensive Care, e.g. for imaging or surgery. During these periods of downtime there is no CRRT clearance and therefore the actual (or delivered) CRRT clearance may be considerably lower than prescribed.

Thus dosing of antibiotics should take into account changes in patient characteristics such as volume of distribution and changes in non-renal clearance, the killing characteristics of the antibiotic, the minimum inhibitory concentration of the target organism, the effluent rate and saturation or sieving coefficient as well as the fact that ~~-~~these coefficients may change with acute phase changes in plasma protein concentrations. Given this, it is not surprising that non-individualized dosing results in a large proportion of patients being either under or overdosed [9-11] resulting in calls for more individualized dosing [9,12-14]. In our previous review we proposed an individualized approach based on both pharmacokinetic and microbiological considerations. We recommended an initial dose based on the published volume of distribution and subsequent doses be based on an estimate of total clearance - total clearance being the sum of residual renal clearance, non-renal non-CRRT clearance and CRRT clearance. We proposed that CRRT clearance should be calculated using the equations given above and data obtained from critically ill patients. This approach, like all other dose adjustments for CRRT, has not been formally validated. Nevertheless, since our previous review other authors have advocated a similar approach [15-17] and recent data provide some supportive evidence.

Prescription of initial loading dose and subsequent maintenance doses

Our recommendation is to base the initial dose on the published volume of distribution of each specific antibiotic in critically ill patients and the target concentration of that antibiotic. As volume of distribution is either unchanged or increased in the critically ill, this will lead to patients receiving at least the standard dose of antibiotic. Dosing that does not take into account changes in volume of distribution will lead to low initial serum concentrations [18].

Furthermore if our method of estimating CRRT clearance is correct then total clearance, half life and serum concentrations will be dependent, to some extent, on effluent rate. Yamamoto et al found that ratio of predicted clearance (based on an in vitro measurement of unbound fraction and effluent rate) to actual clearance ranged from 0.67 to 1.5[16]. Beumier et al found that serum concentrations of meropenem, ceftazidime, cefepime and piperacillin-tazobactam were correlated with effluent rate despite the fact that only the initial drug dose was fixed (subsequent doses were adjusted according to serum concentrations)[11]. Similarly, effluent rate has been shown to be associated with piperacillin clearance [7], doripenem clearance [19] and vancomycin serum concentration [20]. Jamal et al systematically reviewed the literature and demonstrated that CRRT clearance of meropenem, piperacillin-tazobactam and vancomycin is associated with the effluent rate[21]. However, this finding needs to be interpreted with some caution. In some cases CRRT clearance was derived from the equations given above and therefore CRRT clearance and effluent rate would have been mathematically coupled. In contrast, Roberts et al found that trough concentrations of meropenem, piperacillin-tazobactam, vancomycin and ciprofloxacin were not associated with effluent rate[10]. However, the dose of drug given was at the discretion of the treating clinicians who may have taken the effluent rate into account. Udy et al also found there was no relationship between clearance and CRRT settings[22].

Pharmacokinetic data to calculate an appropriate initial dose and to estimate non-renal non-CRRT clearance and CRRT clearance were given in our previous review and on our website (http://www.aic.cuhk.edu.hk/web8/PK_data.htm). Relevant pharmacokinetic data published since 2009 are summarized in table 1~~2~~. As antibiotic clearance by healthy kidneys is usually higher than clearance

by CRRT, subsequent (maintenance) doses of renally excreted antibiotics should generally be decreased. However, colistin may be an exception, as described below.

Dosing of Colistin and Daptomycin

When we last reviewed the literature there was minimal in vivo data to guide prescribing of either colistin or daptomycin and we will therefore concentrate on these two agents. Dosing of colistin poses a particular challenge as the optimal pharmacokinetic/pharmacodynamic relationship is yet to be defined and there are limited pharmacokinetic data to guide dosage. It is usually administered in the form of a prodrug, colistin methanesulfonate, a proportion of which is hydrolyzed to the active compound, colistin. In patients with normal renal function colistin methanesulfonate is eliminated mainly by glomerular filtration with additional clearance contributed by tubular secretion. Colistin is filtered in the glomerulus but is extensively reabsorbed in the tubules so little is eliminated by the kidney. The actual mechanism of elimination is still not yet fully understood [23]. Both colistin methanesulfonate and colistin are eliminated by CRRT. In the case of colistin methanesulfonate, clearance by CRRT will be less than by healthy kidneys while for colistin clearance will be greater than by healthy kidneys. The net effect on colistin serum concentration should depend on the effluent rate. At high effluent rates the rise in colistin methanesulfonate concentration should be small and the clearance of colistin should be high and as a result it may be necessary to increase the maintenance dose. Conversely with low effluent rates it may be necessary to decrease the maintenance dose. This, assumes, however that non-renal clearance is unchanged in renal failure. Unfortunately there are only limited pharmacokinetic data available and neither the effect of renal failure on non-renal clearance nor the effect of effluent rates on serum concentrations have been systematically studied.

In patients receiving CRRT with effluent rates of 2.1 – 3.4L/h a reduced dose of colistin (2 million units 8 hourly) produced sub-optimal serum concentrations, leading the authors to suggest that dose reduction is not required and higher than standard doses should be considered [24]. Similarly in patients receiving CRRT with an effluent rate of 1.9-2.3L/h, Markou et al demonstrated that doses ranging from 1 million units 8 hourly to 2 million units 18 hourly produced sub-optimal serum colistin concentrations[25].

Significant colistin elimination may occur as a result of adsorption to haemofilter and dialysis membranes. Karanen et al demonstrated extracorporeal clearance of 4.33 l/h which was in excess of the effluent rate (2.1-3.4 L/h)[24]. This cannot occur with haemodiafiltration alone, suggesting that adsorption occurred. Similarly in Markou's study the clearance of colistin by haemodiafiltration was only 0.67-0.81 L/hour but overall extracorporeal clearance was 1.83-1.93 L/h~~r~~[25]. Leporati et al reported large difference in pre and post-filter serum colistin concentration. Thus, significant adsorption appears to occur but the factors which determine the extent of colistin elimination by adsorption are unknown, complicating attempts to dose appropriately [26].

~~In~~ In view of the uncertainty regarding colistin pharmacokinetics combined ~~Together with the unknown~~uncertainty regarding the optimal pharmacokinetic / pharmacodynamic~~s target for colistin, theoretical dosing based on calculation~~target we do not recommend calculating a dose but suggest giving at least the recommended dose for patients with normal renal function (3 million units 8 hourly) for patients receiving ~~is not possible. We do not recommend a~~reducing the dose of colistin ~~of at least~~to ~~less than 3 million units 8 hourly (recommended i.e. dose for patients with~~has normal renal function) for

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~~patient receiving~~ CRRT with effluent rates~~within the range~~ of 2.1– 3.4L/h. Other authors have suggested a more aggressive regime of a loading dose of 9 million units, followed by a maintenance dose of up to 4.5 million units 8 hourly, without the risk of toxicity[27].

Daptomycin exhibits concentration dependent kill characteristics. For susceptible *Staphylococcus aureus* with a ~~-~~MIC of 0.5mg/L, a Cmax/ MIC ratio of 100–400, which corresponds to peak plasma concentration of 50–200 mg/l, is required[3]. The peak concentration achieved will depend predominantly on the dose and the volume of distribution. Peak concentrations achieved in critically ill patients receiving 3-8 mg/kg doses were sub-optimal in the majority of patients [3,4,28-31] presumably as a result of a volume of distribution that is approximately 2-3 times the volume of distribution in healthy volunteers [4,29]. The dosing interval will depend on the target trough concentration and the clearance of daptomycin. Elevated creatinine kinase, the major dose-related adverse effect, is more common when trough concentrations exceed 24.3 mg/l [32]. In healthy volunteers approximately 50% of a dose is eliminated by non-renal mechanisms and this does not appear to increase in critically ill patients receiving CRRT [28]. Daptomycin is removed by CRRT with a mean (SD) saturation coefficient of 0.13 (±0.05). Although CRRT clearance was found to be similar to renal clearance in healthy volunteers, the mean (SD) effluent rate of 36.7 (±13) ml/kg/h was high and clearance would be lower if the effluent rate was decreased[28].

In view of its kill and toxicity characteristics~~order to optimise the pharmacokinetic / pharmacodynamic target~~, d~~D~~aptomycin ~~dosing~~ should be dosed using~~based on~~ an extended interval dosing regime. Using ~~According to~~ the information and formulae above, ~~and with the use of formula contained in the previous section and~~ the method detailed in our previous publication [1]~~[ref]~~, a~~the~~ minimum ~~idealtheoretical~~ dose and dosing interval ~~required~~ can be calculated. F~~Daptomycin f~~or *Staphylococcal aureus* blood stream infection with MIC of 0.5 mg/L for a 70kg patient with anuria on CVVHD using a Polysulfone filter and with targeted total effluent of 35 ml/kg/hour, a ~~should be theoretically prescribed as~~ loading dose of 800mg daptomycin with subsequent maintenance dosing interval of 34 hours should~~to~~ achieve a Cmax/MIC of 100 and minimise~~ing~~ the risk of adverse effects~~. .~~(Figure 1). However

i~~t~~t is important to appreciate ~~-~~this calculated ~~e theoretical~~ dose ~~calculated (11.5mg/kg) should also take into account the risk of toxicity and~~ may need~~need~~ to be reduced ~~to~~ in order to comply with dose range approved by regulatory authorities. It is of interest to note that healthy individuals receiving d~~D~~aptomycin at doses up to 12mg/kg daily for 14 days did~~have~~ not develop~~ot been associated with adverse~~ electrocardiographic or electrophysiological evidence of muscle or nerve toxicity[33].

Use of Therapeutic Drug Monitoring (TDM)

From the above it should be apparent that while it is possible to use published data and calculations of CRRT clearance to guide dosing, considerable uncertainty remains. For example volume of distribution of many antibiotics may vary considerably between patients, as may saturation and sieving coefficients (table 1~~2~~). Furthermore changes in hepatic function, which are difficult to monitor clinically, may result in changes in non-renal non-CRRT clearance. As a result, use of therapeutic drug monitoring may be useful to adjust dosing regimes and are a routine part of care of patients receiving beta lactams and CRRT in some intensive care units [34]. Infusion rates are increased or decreased to achieve the desired target concentration depending on the result, which does not need to be available immediately. In practice, a change is required in 74% of cases, even in an ICU with expertise in antibiotic

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pharmacokinetics and dosing [35]. In the future it may be possible to combine therapeutic drug monitoring with sophisticated pharmacokinetic models, which take into account the variability described above, to generate more appropriate individualized antibiotic dosing regimes [6].

Conclusions

In summary the need to target pharmacokinetic end-points means that antibiotic dosing should take into account pharmacokinetic changes associated with critical illness, acute renal failure and CRRT. In general the volume of distribution of antibiotics is increased or unchanged in this group of patients. As a result initial doses should generally be increased or unchanged. Subsequent doses should be based on drug clearance, which will depend on residual renal clearance, non-renal non-CRRT clearance and delivered (as opposed to prescribed) CRRT clearance. As CRRT does not generally fully compensate for the reduction in renal clearance, maintenance doses should be decreased or unchanged. Once appropriate doses have been estimated further adjustment may be made based on the results of therapeutic drug monitoring. Future directions should include the conduct of large scale ~~multi-centre~~ studies of patients receiving CRRT with creation of ~~appropriate~~ pharmacokinetic models which can be used to generate recommendations on dosing changes in response to the results of therapeutic drug monitoring~~ling to account for the abovementioned variabilities~~. This should ~~further~~ be accompanied by development of therapeutic drug monitoring ~~technique~~ with a rapid turn-around time to allow prompt adjustment.

Reference

*Special interest

**Outstanding interest

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Figure legend

Figure 1. Calculation of daptomycin dose

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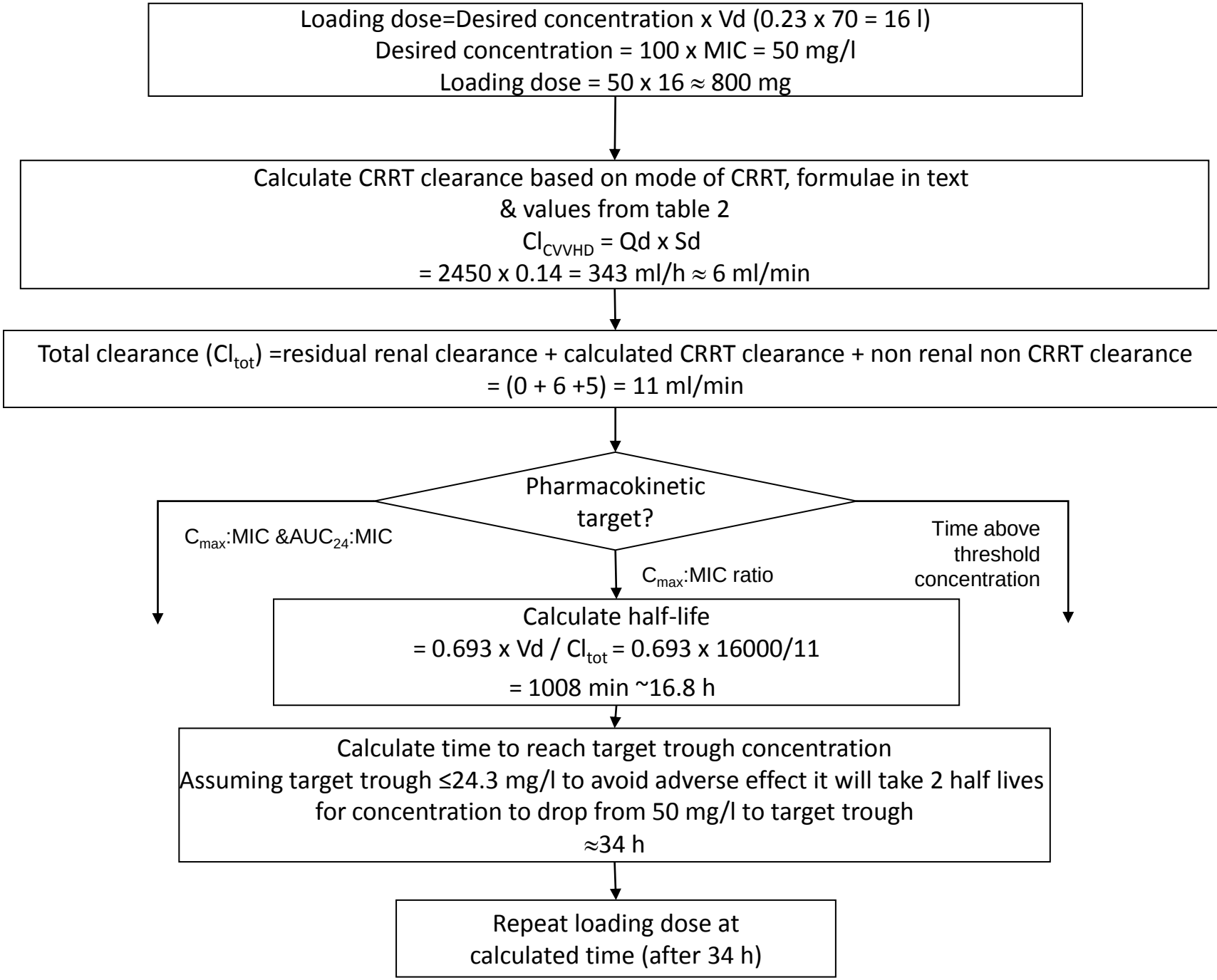
Figure


Loading dose=Desired concentration x Vd (0.23 x 70 = 16 l)
Desired concentration = 100 x MIC = 50 mg/l
Loading dose = 50 x 16 ≈ 800 mg
Calculate CRRT clearance based on mode of CRRT, formulae in text
& values from table 2
Cl_CVVHD = Qd x Sd
= 2450 x 0.14 = 343 ml/h ≈ 6 ml/min
Total clearance (Cl_tot) =residual renal clearance + calculated CRRT clearance + non renal non CRRT clearance
= (0 + 6 +5) = 11 ml/min
Pharmacokinetic target?
C_max:MIC &AUC_24:MIC
C_max:MIC ratio
Time above threshold concentration
Calculate half-life
= 0.693 x Vd / Cl_tot = 0.693 x 16000/11
= 1008 min ~16.8 h
Calculate time to reach target trough concentration
Assuming target trough ≤24.3 mg/l to avoid adverse effect it will take 2 half lives
for concentration to drop from 50 mg/l to target trough
≈34 h
Repeat loading dose at
calculated time (after 34 h)

Table

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