KDIGO Controversies Conference
Drug Prescribing in Kidney Disease:
Initiative for Improved Dosing

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Section 2: Assessment of organ function for drug dose adjustment
Stuart Goldstein & Frieder Keller

The organ probably most impacting drug kinetics is the kidney. Fortunatley, there is a close correlation between the function of the glomeruli and of the tubuli. Impaired tubule function by for example acute kidney injury and tubule necrosis will be accompanied by impaired glomerular filtration. Impaired glomerular function by for example rapidly progressive glomerulonpehritis will impact tubular secreation, metabolism and reabsorption of drugs in parallel. Thus, the glomerular filtration rate (GFR) has been established as a global measure of kidney function.

Selective tubular alterations are rare with some exceptions. For example the tubular creatinine secretion is decreased by cimetidine or co-trimoxazole. The tubular secretion of anionic drugs such as penicillin or cidofovir is inhibited by probenecid. Known inhibitors of the organic cation transporters are cimetidine, ranitidine and tyramine. Except for such drugs, the tubule function can be subsumized under the GFR.

Several methods are available to estimate the glomerular filtration rate (GFR) as a measure of the kidney function in the individual patient. (1) The endogenous creatinine clearance is considered anachronistic due to errors with the urine collection and due to the 24 hours delay in the measurments results.[1] (2) The inulin clearance is propagated as golden standard but rarely performed except for research purposes. (3) Radiocontrast agents like iothalamate are no ideal standard for GFR measurements since an extrapolation of the half-life or of the area under the curve AUC is needed. Such extrapolation is the less complete and less reliable the more the kidney function is impaired and the more prolonged the half-life is.[2] (4) The isotope GFR measurments are not practical for individual drug dose calculations since they are expensive and no everywhere and everytime available. (5) The most practical and valuable measures of the GFR are the urine-freee methods based on serum creatinine and specific other variables. The different urine-free methods to estimate the GFR have different advantages and disadvantages that we should like to discuss here.

GFR Estimates

For drug dose adjustment the kidney function should be estimated by the GFR. With all of the available methods the independent variable, the GFR is estimated from the dependent but measurable variable the serum creatinine (Screa). To convert the serum creatinine from mg/dl to mcmol/l multiplication by the factor of 88.4 is needed (SCrea[mcmol/L] = 88.4 x SCrea[mg/dL]).

It is important to note that in the last years the Jaffe method to estimate the serum creatinine has been replaced by the new calibrated isotope dilution mass spectrometry technique (IDMS) yielding serum creatinine estimates that are 5% lower on average than previously. This must be considered when using equations that have been established based on the creatinine measured by the Jaffe method (SCrea[IDMS] = 0.95 x SCrea[Jaffe]).
The most frequently used urine free method is the Cockcroft and Gault equation (C&G).[3] This equation primarily estimated the creatinine clearance from serum creatinine and age and is used now as an GFR estimate.

$$GFR = \frac{140 - Age(years)}{0.82 \cdot Screa(\mu mol/L)} \cdot Weight(kg) \cdot 0.85(female)$$

The frequently used C&G equation has been validated recently for the new calibrated creatinine. This new equation does not have a coefficient and is more easily to memorize and to use for calculations than other GFR estimates.[4] It is an advantage of the coefficient-free C&G equation for individual drug dose adjustment that the body weight is considered. Treating overweight patients, however, the lean body weight should be used.

$$GFR = \frac{155 - Age(years)}{Screa(\mu mol/L)} \cdot Weight(kg) \cdot 0.85(female)$$

For an automatic implementation in the chemical laboratory outprint, the C&G equation is not suitable since the body weight is usually not available automatically. This is the big advantage of the modification of diet in renal disease (MDRD) equation that it is standardized to a body surface area of 1.73 sqm. The MDRD GFR is using the serum creatinine in mg/dl.[5]

$$GFR = 186.3 \cdot Screa^{-1.154} \cdot Age^{-0.203} 1.212[black] \cdot 0.742[female]$$

The MDRD equation can be used for individual drug dose adjustment when the body surface area (BSA) is considered (GFR = MDRD x BSA / 1.73m^2).[6] This very popular MDRD equation has been transformed also for the new IDMS calibrated creatinine measurements since it holds (186.3 x (1 / 0.95)^-1.154 = 175.6).[7]

$$GFR = 175.6 \cdot Screa^{-1.154} \cdot Age^{-0.203} 1.212[black] \cdot 0.742[female]$$

The primary MDRD equation has been validated only for a GFR < 60 ml/min. Therefore, the new CKD EPI equation has been proposed to cover the full range of the chronic kidney disease spectrum.[8]

$$GFR = 141 \cdot \min(Screa / \kappa, 1)^{\alpha} \cdot \max(Screa / \kappa, 1)^{-1.209} \cdot 0.993^{Age} \cdot 1.159[black] \cdot 1.018[female]$$

In the CKD-EPI formula expressed as a single equation the Scr is serum creatinine (mg/dL), κ is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/κ or 1, and max indicates the maximum of Scr/κ or 1 and Age is measured in years. Independent from age, weight, sex, race and muscle mass is the GFR estimate derived from serum cystatin C (nephelometric CystC mg/L) that most simply can be calculated by the Oerebro formula.[9]

$$GFR\_CystatinC = \frac{100}{CystC(mg/L)} - 14$$

It depends on the local experience and availability of data which one of the above equations should be used for assessment of the individual GFR to adjust the drug dose. We think it is more important to have any GFR estimate and to think about dose adjustment than to have a most exact estimate but to not have it in time and without big effort.

The GFR estimates holds for chronic kidney disease. But also in acute kidney injury a measure of individual kidney function is needed to adjust the drug dose. Such a measure can be derived from the GFR equations by taking into account that such estimates are always delayed.[10] In patients with oliguric or anuric kidney failure the GFR is zero.

Liver, Physical Function and Age

In contrast to the kidney function, the liver function cannot be easily quantitated and assessed for drug dose adjustment. The Child-Pugh score lacks the sensitivity to quantitate the specific ability of the liver to metabolize individual drugs.[11] The proposal has been made to use the new MELD score to assess the liver function. Liver failure is considered when the MELD score is 20 or above where the specification is (etiology: 0 if cholestatic or alcoholic, 1 otherwise). However, the MELD score is determined also by the serum creatinine and thus by the kidney function.

$$MELD = +3.8 \cdot \ln[bilirubin(mg/dL)] + 11.2 \cdot \ln[INR] + 9.6 \cdot \ln[SCrea(mg/dL)] + 6.4 \cdot [etiol]$$

Another determinant of drug kinetics and dynamics might be seen when the physical function is impaired. Physical function should be assessed. The Karnofsky performance score (70% weakness, 40% bed-bound) or the frailty index have been proposed to quantitate such co-morbidity and the effects of age. But no systematic correlation to drug kinetics and dynamics has been performed yet. In elderly people there is a loss of kidney function.. This should be assessed by the individual GFR. The effect of age on body composition or liver function is less impressive. We have found age related changes to be most impacting the drug half-life (1.39-fold ± 61%).[12] Contrasting to common expectations drug clearance and volume parameters have been found to be less influenced by aging processes (Tab. 1).

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Table 1.

Effect of age (> 65 years) on pharmacokinetic parameters, namely half-life (T1/2), clearance (Cl) and volume (Vd) according to our NEPharm database analysis.[12]

Drug	Median change (%)		
	T1/2 (hours)	Cl (ml/min)	Vd (liter)
Analgesic (N = 11)	+31%	+35%	+22%
Antiarrhythmics (N = 4)	-3%	+1%	+37%
Antiînfective agents (N = 39)	+45%	+8%	+7%
Antihypertensive agents (N = 11)	+9%	+2%	+19%
Central nervous system agents (N = 38)	+29%	+11%	+3%
Cyctostatics (N = 8)	+23%	+14%	+121%
Others (N = 26)	+23%	±0	±0
Total (N = 137)	Overall arithmetic mean ± SD of changes		
	T1/2 (hours)	Cl (ml/min)	Vd (liter)
	+39% ± 61%	-1% ± 54%	+24% ± 56%

Section 3: Calculating drug doses in CKD
Darren Grabe and Lesley Stevens

Introduction

Calculation of drug doses in patients with kidney disease is complex.[1-3] The challenge is to integrate the pharmacokinetic profile of a drug with an accurate estimate of the patient's kidney function in the context of the specific clinical scenario including potential for adverse events relative to too high, or too low, a dose.[4,5] Despite numerous published guidelines[6-13] regarding drug dosing, we have not yet succeeded in determining best methods to calculate drug dosages for particular patients as evidenced by the high rate of adverse events and drug related morbidity and mortality.[14-16]

Currently, adjustment of drug dosages is performed based primarily upon the package inserts. In most cases, the pharmacokinetic studies were conducted when the drug or the relevant metabolites are cleared by the kidney and have a narrow therapeutic window.[17,18] In that regard, the glomerular filtration rate (GFR) or its estimate is assumed to capture all aspects of the effect of kidney disease on the pharmacokinetic profile of a drug under the "intact nephron hypothesis."[19] The problem arises is that both dosing guidelines as well as clinicians' application of these guidelines to individual patients, do not explicitly incorporate other factors that while may not correlate with GFR (e.g. decreased absorption or hypoalbuminemia), may be present in patients with kidney disease.[5,20-22]

Impact of Kidney Disease on Pharmacokinetics

Pharmacokinetic parameters The most apparent alteration of CKD on drug pharmacokinetics is the reduced clearance of the drug or its metabolite due to a reduction in GFR with subsequent accumulation of drug or relevant metabolites. However, kidney disease is associated with a number of other factors which may influence drug dosing and include changes in absorption[5,22], first-pass metabolism, hepatic metabolism[23], drug transport[20], protein binding[24] and volume of distribution[25] (Table 1). The impact of these other factors on drug dosing is unclear and deserves attention and further study.

Table 1: Impact of CKD on Pharmacokinetics

Pharmacokinetics Parameters	Kidney Disease Effects	Incorporated into Drug Dosage
Absorption	+	N
Intestinal and first pass metabolism	+	N
Distribution	++	N
Clearance		
Renal	+++	Y
Nonrenal	++	N

Assessment of Kidney Function For most drugs, dosing guidelines were developed prior to standardized calibration of creatinine assays and reporting estimated GFR calculated using the Modification of Diet in Renal Disease (MDRD) Study equation (eGFR). The discussion as to which estimate can be used to adjust drug dosages, often centers around which equation, however, it is the issue of the creatinine assay that is most relevant.

Historically, there has been substantial variability in serum creatinine values reported by different clinical laboratory creatinine methods[28]. Pharmacokinetic studies performed using non-standardized creatinine methods obtained results that were dependent upon the particular creatinine method used, leading to substantial variation when translated into practice[29]. Use of standardized creatinine methods will lead to less variation in estimating kidney function

and more consistent drug dosing. However, for drugs for which the studies have already been performed, the kidney function cutoffs, regardless of which equation was used, are likely to be substantially different from those identified in the original study.   Using standardized creatinine, the two most commonly used equations, the Cockcroft and Gault formula and the MDRD Study equation, result in the same drug dosage for most patients[30]. It is important to remember that for all creatinine based equations, the limitations of serum creatinine must be considered[31].

Determination of Drug Dosing Guidelines

Loading Dose Loading doses may be required if a drug has a long half life and is used in situations where there is a need to achieve steady state rapidly. Equation (1) describes the dependence of the half-life on the volume of distribution and the clearance of the drug. Changes in either of those factors can result in an increase or decrease in the half-life. It takes approximately 3.3 half-lives to achieve steady state drug concentrations

$$t_{1/2} = [(0.693)\ (Vd)]/(Cl) \qquad \text{Equation 1}$$

Equation (2) describes how the loading disease is related to the desired initial concentration of the drug) and the volume of distribution.

$$\text{Loading dose} = (C_{initial})\ (V_d) \qquad \text{Equation 2}$$

Equation 3 indicates how a modified loading dose can be calculated given known changes in volume of distribution.

$$\frac{\text{Usual loading dose}}{\text{Modified loading dose}} = \frac{\text{Normal } V_d}{\text{patient's } V_d} \qquad \text{Equation 3}$$

Most published guidelines do not include adjustment in loading dose, despite the well documented changes in volume of distribution that occur in patients with kidney disease.

Maintenance dose The goal of a maintenance dosing regimen is to preserve the steady-state drug concentrations as would occur if the patient had normal kidney function. A change in clearance requires a change in dose to maintain drug concentration (equation 3).

$$\text{Maintenance dose} = (C_{average})\ (Cl) \qquad \text{Equation 3}$$

The strategies that are employed to accomplish this goal include reducing the rate of a continuous infusion, reducing the dose, prolonging the interval between doses, or a combination of these strategies. In general, reducing the dose but maintaining the same frequency of dosing will result in more stable drug levels. However, that may not be appropriate for toxic medications, where achieving low trough levels is the goal. For example, aminoglycoside regimen generally use the strategy of extending the interval between doses.

Bioavailability is another important factor to consider when medications are to be administered orally. However, the impact of impaired kidney function on bioavailability of most drugs is unknown, and may be determinant on fluctuating individual factors such as concomitant drugs or gastric pH, making it difficult to establish a consistent drug regimen.

The final consideration is the effect of kidney replacement therapy. Depending on the modality, dialysis may remove drugs and relevant metabolites either intermittently or continuously. The total clearance of drugs is dependent on residual kidney function, drug and metabolite properties, dialysis properties (e.g. duration) and membrane properties (e.g. pore size). All must be considered in establishment of the maintenance dose.

Determination of Individualized Patient Dose

Calculating drug dosages for individual patients Calculating drug dosage in patients with kidney disease requires consideration of the impact of impaired kidney function on pharmacokinetic parameters. In particular, application of the drug dosing guidelines to an individual patient should be sensitive to the pharmacodynamics of the individual drug that may not be incorporated into the dosing guideline (eg decreased absorption due to use of chelating medications) as well as patient related factors including urgency of the clinical situation, co-morbid conditions, and costs (Table 2). Thus, initial assessment of the patient is critical to obtain relevant information to choose a proper drug, dose and schedule. This initial assessment should include a history, physical examination including weight and an evaluation of volume status, and medication history to identify possible drug interactions. Laboratory data is required to assess kidney function as well as other organ function.

Table 2: Determination of Individualized Patient Dose

Factor	Method of Ascertainment	Modify
Clearance	eGFR/eCrCl	Maintenance
Volume of distribution	Level of drug after initial dose	Loading
Urgency of clinical situation	Clinical judgment	Loading
Impact of fluctuations in steady state levels	Clinical judgment	Maintenance
Patient's financial situation	Clinical judgment	Maintenance
Medication interactions	Profile review	Loading, maintenance

Measurement of Therapeutic Drug Levels For all drugs, the drug dosing guidelines are only appropriate if the conditions are stable. Changes in any of the factors mentioned will require further modifications to individual patient's regimens. Measuring drug concentration may be one way to optimize therapeutic regimens and account for changes in individuals over time. However, therapeutic drug monitoring requires availability of a reliable assay and known correlation of drug concentration to therapeutic and toxic. In addition, hypoalbuminemia may influence interpretation of drug levels as the total drug may be reduced but the active drug may not be reduced. Active drug cannot be measured and therefore clinicians must consider the impact of hypoalbuminemia in interpretation of measured drug concentrations.[20-22]

Conclusion

Calculation of drug doses in patients with CKD is complex and often ignores other relevant factors which may influence outcomes. Changes in the drug clearance associated with reductions in the GFR are expected. However, data outlining the influence of CKD on absorption, transport, non-renal clearance, protein binding and distribution are limited.

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Section 4: Calculating drug doses in AKI
Brian Decker and Deborah Pasko

Calculating drug doses in AKI: An Overview
Deborah Pasko

Introduction
Over the past several years the assessment of kidney function has been through many revisions. First the definition of acute versus chronic kidney failure was established, and then there was a transition from acute renal failure to acute kidney injury. Now within the past couple of years has been the introduction of AKI biomarkers, RIFLE criteria, and the ongoing discussion about Cockcroft-Gault vs MDRD. Despite all of the changes in nomenclature and definitions AKI still affects many patient populations, but the intensive care patient seems to be most vulnerable. The incidence of AKI for intensive care patients, including pediatric patients, can range from 1-25% with mortality rates of 15-60% [1,2,3]. The high mortality rate of AKI can be attributed to multiple physiological changes that occur in these patients. AKI is a constellation of symptoms and can start as minor physiological changes and may manifest into acute failure requiring renal replacement therapy. More often than not patients experiencing any stage of AKI are also receiving medications, some life-sustaining. It is important for clinicians to understand how to manage pharmacotherapy regimens during each stage of AKI in addition to applying pharmacokinetic and pharmacodynamic principles so medication regimens can be optimized and kidney function can be protected.

Applying pharmacokinetic principles in AKI
The application of basic and complex pharmacokinetic principles involving changes in absorption, distribution, metabolism, and excretion is the first step to optimizing drug therapies for patients with AKI. Critically ill patients typically have minimal oral intake of food and liquids and rely upon intravenous fluids and for fluid maintenance and nutrition. In addition H2-antagonists and proton pump inhibitors are used for stress ulcer prophylaxis and significantly alter the gut pH to either neutral to slightly basic. Any orally administered drug needing an acidic environment may not be readily absorbed and may not be effective. Other absorption alterations may include slow GI motility, prolonged intestinal transit times, bacterial colonization, and necrotizing enterocolitis (seen in neonates). Intravenous administration of drugs for patients with AKI may need to be considered to assure appropriate absorption.

Drug distribution is one of the most important, but yet the most complicated, pharmacokinetic principle to understand for patients with AKI. There is a fine balance between adequate hydration for kidney perfusion and total body fluid overload. There have been numerous studies conducted about the impact of fluid overload on patients with AKI, both adult and pediatric [4,5,6,7,8]. These studies have concluded that critically ill patients should initially be managed in a slightly negative fluid balance after initial adequate fluid resuscitation has been achieved [9].This can be achieved by three strategies: 1) fluid restriction, 2)diuretic therapy, and 3) renal replacement therapy. Fluid restriction in critically ill patients is often difficult because of the needed fluid to deliver drugs and nutrition. Diuretic therapy has been the mainstay of therapy for patients initially, however studies now suggest once patients reach a fluid overload status >5% renal replacement therapy should be considered, and that continual use of diuretics may have a negative impact on patients [10,11]. Any combination of these three fluid management strategies may cause rapid or constant fluid removal and will significantly affect the distribution of drugs. For drugs that normally have small volumes of distribution (Vd) any increase or decrease in fluid volume in the patient will cause a substantial dose adjustment for that drug. An example of this is aminoglycosides which normally have a Vd of approximately 0.2-0.35 L/kg in a euvolemic patient and is a peak/mic-dependent drug. If initial serum concentrations are, for example, 8 mg/L for a peak concentration, and 1 mg/L for a trough with a Vd of 0.25 L/kg, then doubling of the Vd to 0.5L/kg will result in a peak of 4 mg/L and trough of 0.5 mg/L. At this point the drug has a decreased area under the curve for the peak serum concentration and will have approximately half of the killing effect on bacteria. In contrast if the fluid overloaded patient has a peak of 8 mg/L and a Vd of 0.5L/kg and the fluid is removed and the Vd decreases to 0.25L/kg then the peak serum concentration is now 16 mg/L, and the trough concentration would be 2 mg/L.

Fluid shifts such as these can happen within minutes to hours for patients with AKI. Constant re-evaluation and monitoring of the drug therapies, including frequent assessment of serum concentrations is warranted. Drugs that have larger volume of distributions are less affected by fluid shifts and require less monitoring unless they have a very narrow therapeutic window. Moreover, another key component of drug distribution is protein binding. Patients with AKI can experience protein losses and/or not enough protein intake, and alterations in protein binding when in a uremic state. In addition any administration of blood and/or albumin products will also affect the drug protein binding. Again, frequent monitoring is needed, especially when using highly protein bound anticonvulsants, such as phenytoin. The next pharmacokinetic category is metabolism and will be explained in much greater detail in the second half of the manuscript.

The final pharmacokinetic parameter, and probably the most studied in patients with AKI, is excretion, or elimination. Despite multiple studies however, there is still controversy about what equation most accurately determines glomerular filtration rate (GFR) in patients with AKI [12,13]. The options include the standard Cockcroft–Gault, Jeliffe, or modified Jeliffe, and more recently the Modification of Diet in Renal Disease (MDRD) [12]. The gold standard equation for pediatric patients is still the Schwartz equation. Historically, all drug studies have been based on assessing creatinine clearance or GFR [14]. There is now emerging discussions however about using MDRD as the equation to estimate kidney function for drug dosing [15]. Most of these equations involve the use of creatinine, which is known to be a late marker in AKI. Instead, maybe drug dosing for patients with AKI needs to take a different approach. There are now more sensitive early biomarkers, such as NGAL, cystatin C, interleukin 18, and kim-1 [16], that could be used in conjunction with the RIFLE [17] and pRIFLE [18] criteria to better predict when to make adjustments in drug therapy regimens. There is also a better understanding of the pathogenesis of progressive kidney disease [19]. These three approaches could be used in combination to proactively suggest changes in drug doses and/or intervals early on, during the risk phase instead of waiting until injury occurs and then retroactively making changes to the drug regimens. For example if the patient enters the first stage of AKI assessed by a drop in urine output and biomarkers are elevated then the medication list should be reviewed for any nephrotoxic medications that should either be discontinued, changed to another therapy, or be dose adjusted. Examples would include holding, decreasing dose, or extending intervals of drugs including aminoglycosides, vancomycin, teicoplanin, methotrexate, antivirals (acyclovir, ganciclovir, foscarnet) until further assessment of renal function could be made. This approach may aid in protecting, or preserving current renal function. This approach, however, has never been studied and would need further clinical trials to determine the usefulness of such an approach.

Clinical pearls and recommendations
Drug dosing in AKI differs from CKD from several perspectives. The most important points surround a balance of knowing when to give more of a drug based on Vd and/or clearance in comparison to giving less. The previous aminoglyoside example demonstrates how important increasing the dose based on the current Vd, despite if the patient is having worsening renal function. Doses may need to be increased but intervals further extended to prevent accumulation. For patients with AKI less is not always better. This is especially true when dosing antibiotics in patients with AKI. Calculating drug doses in patients with AKI may seem complicated. Principles to use include the use of standard pharmacokinetic equations, therapeutic drug monitoring (when available) and frequent assessment of fluid status and renal function of the patient. In addition for drugs requiring continuous administration (pressors, opioids, etc) and titration these agents should just be titrated base on desired physiological outcomes and should not be adjusted based on fluid status, unless significant fluid changes have occurred.

Another component that clinicians typically forget or fully do not understand is the non-renal clearance of drugs. This aspect of drug metabolism and elimination is significantly altered in AKI and physiological shifts can occur that may also necessitate higher dosing of certain agents. Understanding non-renal clearance can also aid clinicians to optimize drug therapies for patients with AKI.

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Section 4: Calculating drug doses in AKI (continued)

Calculating drug doses in AKI: Impact of non-renal clearance
Brian Decker

Introduction

It has been well established that the attenuation of the critical clearance processes of glomerular filtration and tubular secretion observed in acute kidney injury (AKI) and chronic kidney disease (CKD) hinder the excretion of renally-eliminated drugs. For CKD the literature that describes these processes and the disposition of renally-eliminated drugs is robust leading to the development of specific drug dosing algorithms to guide pharmacotherapy in patients with CKD and ESRD patients receiving hemodialysis. However, this is not true for AKI; clinically reliable drug dosing algorithms for AKI have remained elusive. This is likely due to the quite variable magnitude and physiological milieu of AKI which makes the research and prediction of drug disposition exceedingly more difficult. In addition, the underlying paucity of adequate tools to accurately determine renal function in the acute setting is a contributing factor. Moreover, this pharmacotherapeutic approach of focusing solely on renally-eliminated medications in renal failure patients is incomplete because it neglects non-renal clearance. This is clinically significant because emerging *in-vitro* animal and human studies have shown that nonrenal clearance, dominated by hepatic CYP450-mediated metabolism, is diminished by the toxic, uremic environment found in renal failure. Administering the usual, full dose of a metabolized medication to a renal failure patient may involve a similar risk for drug toxicity as administering the full dose of a renally-eliminated medication. However, drug toxicity is not the only concern as it is conceivable that the metabolic transformation of pro-drugs to their active forms could also be inhibited by uremic solutes. Complicating matters further, the fluctuating concentrations of uremic solutes in a patient receiving hemodialysis likely results in periods of both high and low drug metabolism making predictions of drug action and disposition even more difficult. With notable exceptions, the majority of the current research investigating non-renal clearance in AKI and CKD utilizes *in-vitro* and animal models. Within the AKI literature there appears to be disagreement with the majority of animal studies showing no effect on CYP450-mediated metabolism from AKI and the human studies demonstrating decrements in nonrenal clearance from AKI. The purpose of this summary is to describe what is known regarding AKI and non-renal clearance, to provide recommendations for dosing metabolized medications in AKI and to outline potential avenues for further research.

AKI and CYP450- mediated metabolism

The literature describing non-renal clearance in CKD has repeatedly shown that uremic solutes have an inhibitory effect on CYP450-mediated metabolism. Multiple animal and the few human studies have demonstrated a reduction in the transcription and/or metabolic activity of hepatic and intestinal CYP450 enzymes by uremic solutes in CKD [1-15, 46-48]. This contrasts with the literature describing the impact of AKI on non-renal clearance which surprisingly shows that in the majority of animal studies no effect on CYP450- mediated metabolism from AKI. Of the current 13 studies that examined the effect of AKI on hepatic drug metabolism using various medication probes, nine studies did not demonstrate any impact on hepatic metabolic activity [16-18, 21-26, 45]. The remaining four studies varied showing both an increase and a decrease in hepatic metabolic activity from AKI [19, 20, 27, 28]. Similarly, three animal studies of AKI on the activity of specific CYP450 enzymes did not demonstrate any effect for the majority of CYP450 enzymes examined (CYP2A1, 2B1/2, 2C11, and 2D2) [29-31]. However, the effect on some of the CYP450 enzymes in these studies, specifically 2C6 and 3A2, appeared to depend on the animal model of AKI utilized as these enzymes showed either no change or a reduced metabolic activity. Interspecies differences were also observed even when the same medication probe was used. A rat study of diltiazem utilizing the uranyl nitrate model of AKI resulted in an increase in hepatic metabolism [19]. Conversely, a rabbit study using the folate model of AKI and diltiazem showed reduced hepatic metabolism [20]. Four human studies of AKI and nonrenal clearance, however, appear to refute the majority of these animal study findings. A study by Macias et al. evaluating the pharmacokinetics of vancomycin in human AKI subjects receiving continuous venovenous hemofiltration found that nonrenal clearance appears to decrease with the

duration of renal failure. Nonrenal clearance of vancomycin was initially preserved early in the course of AKI, but eventually approached the clearance observed in patients with CKD [49]. Similar results were also found in two other AKI studies of continuous hemofiltration and imipenem by Mueller et al. and Vos et al [50, 51]. It is not known precisely what constitutes the nonrenal clearance in these studies, as drug metabolism and clearance can occur in a variety of organs beside the liver. However, if the nonrenal clearance is primarily hepatic the results are compelling; presumably the accumulation of uremic solutes over time lead to an inhibition of the nonrenal clearance. Another human study of AKI and hepatic metabolism by Heinemeyer et al. evaluated the pharmacokinetics of the NSAID, metamizole and its primary metabolite monomethyl-aminoantipyrine (MMAAP) in critically-ill patients with AKI [32].   These researchers found significantly reduced clearance of MMAAP in patients with AKI versus normal renal function suggesting decreased hepatic metabolism. However, they cautioned that definitive conclusions on the pharmacokinetics of metamizole and likely other metabolized medications in AKI remain hampered by the clinical complexity and potential confounders in the critically-ill patient. Hypoxia, decreased protein synthesis, competitive inhibition from concomitant medications and decreased hepatic perfusion could also be explanations for the reduced clearance of the primary metabolite in this study. In addition, though metamizole has been shown to be an inducer of CYP450 2B6 and 3A4, and its secondary metabolite 4-methylaminoantipyrine undergoes an enzymatic metabolism to 4-amino-antipyrine when incubated with human liver microsomes, no specific CYP450 isoenzyme has been identified that governs the metabolism of metamizole or its metabolites [44].

AKI and drug transport
Drug transporters are found in a variety of tissues including the liver, kidney, intestine, brain and placenta and are classified broadly into two major classes, efflux and uptake [37]. Efflux transporters function to excrete drugs from within cells to the extracellular space often against a concentration gradient. Conversely, uptake transporters facilitate the translocation of drugs into cells such as hepatocytes where metabolism can occur. Similar to the literature for CYP450 enzymatic activity, animal studies of drug transporters in CKD have shown reduced transporter expression and activity when compared to animals with normal renal function [41-43, 48]. The decreased transporter activity and expression is postulated to be secondary to uremic solutes and would be expected to have a significant clinical impact on the disposition of metabolized medications. In CKD, the two critical drug transporters that have been studied the most are p-glycoprotein (P-gp), an efflux transporter and organic anion transporter (OAT), an uptake transporter. Unfortunately, there are only a small number of studies evaluating transporter function in AKI. In studies of rats with AKI, there was increased P-gp expression in the kidney, but not in the liver or intestines [33-36]. However, despite the increased P-gp expression in the kidney, clearance of P-gp substrates was reduced. This was also observed in the liver and intestines leading the researchers to conclude that AKI may cause a systemic suppression of P-gp function.   In rat ischemia-perfusion models of AKI and OAT transporters, OAT1 and OAT3 mRNA and protein expression were reduced [38-40]. This resulted in a decreased renal uptake and clearance of the OAT substrate, p-aminohippurate.

Renal replacement therapy and non-renal clearance
Research by Nolin and colleagues demonstrated that a single 4-hour session of hemodialysis increased the nonrenal clearance of erythromycin in human subjects with ESRD [11]. This was presumably secondary to the removal of uremic solutes that accumulate during the interdialytic period and inhibit CYP450 3A4 and drug transporters in combination or independently. A subsequent study by Nolin et al. of midazolam in subjects with ESRD provided further clarity and implicated transporters (hOATP and/or intestinal P-gp) as the likely drug disposition bottle-neck in uremia rather than CYP3A4 [48]. By logical extension, one would expect a similar improvement in nonrenal clearance in AKI patients receiving hemodialysis. However, the continuous hemofiltration research with vancomycin and imipenem implies that this phenomenon may take time to develop as nonrenal clearance initially remained intact in AKI in these studies [49-51]. Furthermore, despite the ongoing removal of the inhibitory uremic solutes by the continuous hemofiltration, nonrenal clearance still declined. This suggests that though there are many variables potentially impacting drug metabolism in a critically-ill patient receiving continuous hemofiltration, there may be limits to the magnitude of improvement in nonrenal clearance that can be expected from a renal replacement therapy.

Drug dosing recommendations
It is apparent that drawing any clinically meaningful conclusions from the studies of AKI and non-renal clearance applicable to drug dosing decisions in humans would be premature. Though the majority of the animal studies of AKI showed no effect on CYP450-mediated metabolism, the animal research on specific drug transporters did demonstrate a decrement in transporter function from AKI. Moreover, the few human AKI studies appear congruent with the CKD literature and support a negative effect on nonrenal clearance. There are several potential methodological issues within the animal studies, however, that may explain the discrepancies between the animal and human data. For one, the animal models of AKI utilized may be affecting hepatic metabolism differently. Interspecies differences may also explain some of the disparate results. Furthermore, extrapolating the results of the animal studies of specific hepatic CYP450 enzymes to humans must be done with a degree of caution. Though there are general similarities, animal CYP450 enzymes are not necessarily analogous to human CYP450 enzymes. Individual pharmacogenomic differences can also impact CYP450 enzymes conferring vastly different activities for the same isoenzyme. The effect of AKI on drug metabolism in CYP450 activity in one organ such as the liver also cannot be reliably extrapolated to other organs such as the intestine. Finally, other areas of uncertainty in the literature include the human studies of critically-ill patients. The precise nature of the nonrenal clearance for vancomycin and imipenem is unknown and may not be primarily hepatic. The metabolic pathway of metamizole is also incompletely characterized. In addition, the inherent clinical complexity and medical regimens of the critically-ill subjects with AKI can be profound introducing confounding variables that may have influenced drug disposition.

Given the current uncertainty, the clinical approach to AKI patients receiving metabolized medications should include frequent monitoring of drug response and where possible pharmacokinetic analysis of serum concentrations of medications. Unfortunately, therapeutic drug monitoring is not always possible in the clinical setting since serum concentrations of many of the metabolized medications are not routinely obtained or available. The concurrent development of tests that are can provide drug concentrations for our most critical metabolized medications in a clinically relevant time frame is needed. In addition, the duration of AKI appears to be an important issue and should be considered when dosing medications with significant nonrenal clearance. The practice of using the CKD and ESRD dosing recommendations for medications with a component of nonrenal clearance may lead to subtherapeutic levels early in the hospital course of an AKI patient when nonrenal clearance remains largely intact. As a result, larger doses of a medication early in the course of AKI may be appropriate with the caveat that the dose should be reduced with time as the AKI persists and nonrenal clearance attenuates.

Future research directions
There are several potential areas for future research for AKI and non-renal clearance. To start, some very fundamental and critical questions are still seeking answers that could help elucidate drug disposition in AKI. These include how to accurately and reliably determine both renal and hepatic function in AKI. In addition, given the potential confounders present in animal models of AKI and CYP450 metabolism, more human studies are certainly needed. Further investigations of the impact of renal replacement therapy such as hemodialysis on hepatic metabolism in the acute setting are also necessary. The elucidation of the nonrenal clearance component of our important medications is also warranted. For now and for unknown reasons, the balance of the emerging animal AKI literature departs markedly from the CKD research and seems to support the conclusion that AKI does not impact CYP450-mediated metabolism. Conversely, the impact of AKI on drug transport and the studies of vancomycin and imipenem and nonrenal clearance agree with the CKD studies. However, the nascent nature of this area of AKI research, the limitations of the existing animal studies and the scant human trials make these statements less reliable and potentially ephemeral.

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Section 5: Drug Removal by Intermittent Renal Replacement

A. J. Atkinson and Jason G. Umans

Hemodialysis removes many small molecule drugs to a significant extent. Consequently, optimal pharmacotherapy of patients on chronic hemodialysis and emergency hemodialysis for some patients who have received drug overdoses are both critically dependent on the availability of reliable information from well-designed and executed pharmacokinetic studies. From the standpoint of pharmacokinetics, the artificial kidney is an ideal eliminating "organ" because, in contrast to renal or hepatic routes of drug elimination, blood flow to the eliminating organ, drug concentrations in blood entering and leaving the eliminating organ, and recovery of eliminated drug can all be measured in routine studies (**Figure 1**) (1).
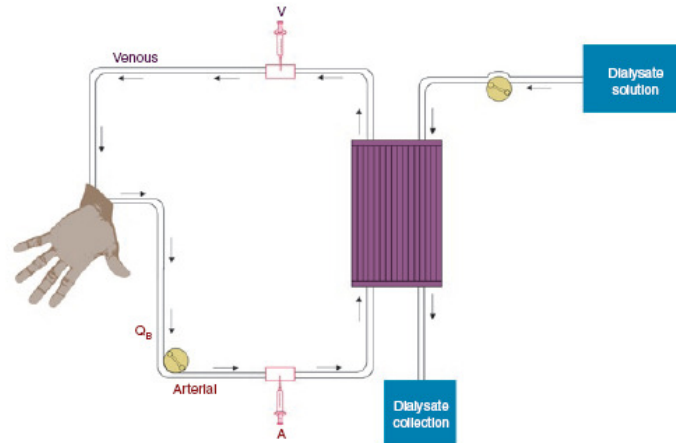

Figure 1. Sources of data for analysis of hemodialysis pharmacokinetics include drug concentration in blood or plasma entering (A) and leaving (V) the dialyzer, blood flow through the dialyser (QB), and drug removal in the spent dialysate (reproduced from reference 1).

Unfortunately, the accuracy of many studies of hemodialysis pharmacokinetics is compromised because they do not incorporate all of these measurements in their analysis or because they use them without consideration of additional factors such as the partitioning of drug between plasma and erythrocytes.

Hemodialysis clearance:

Accurate estimation of hemodialysis clearance is of paramount importance in the conduct of pharmacokinetic studies in hemodialysis patients. Elimination clearances are additive, so total drug clearance during hemodialysis (CL_E) can be expressed as the sum of a patient's residual renal clearance (CL_R), nonrenal clearance (CL_{NR}), and dialysis clearance (CL_D):

$$CL_E \;=\; CL_R + CL_{NR} + CL_D \tag{1}$$

Levy (2) proposed an arbitrary but reasonable threshold criterion by assigning significance to dialytic drug clearance when it exceeds 30% of total non-dialytic elimination (i.e., when $CL_D > 30\%$ of $CL_R + CL_{NR}$). However, this comparison needs to be made using clearance estimates that are consistent in that they are uniformly based on either plasma or blood drug concentrations. In addition to CL_D, the extent of drug removal by hemodialysis (i.e., actual mass transfer of drug from blood to dialysate) is determined by the duration of hemodialysis sessions, the contribution of ultrafiltration across the dialyzer, and by drug and patient factors, including drug distribution volume, binding to plasma proteins and partitioning into erythrocytes, and dialysis-associated reductions in intercompartmental clearance (3).

The two approaches generally used to estimate CL_D are termed the **recovery method** and the **A-V difference method** (4). The recovery method has been considered to be the "gold standard" (5). In this method, CL_D is calculated from an equation that is similar to that used to calculate renal clearance:

$$CL_D = \frac{C_D \cdot Vol_D}{\overline{A} \cdot t} \qquad (2)$$

where the amount of drug recovered by dialysis is the product of the drug concentration in dialysate (C_D) and total volume of dialysate (Vol_D) collected during the dialysis time (t), and $\overline{A}$ is the average concentration of drug in plasma entering the dialyzer. The product $\overline{A} \cdot t$ can be replaced by the area under the afferent blood or plasma concentration curve (AUC_A) during hemodialysis. Assumptions that should be confirmed are that all drug removed as blood traverses the dialyzer actually appears in spent dialysate and that there is no drug adsorption to the dialysis membrane as may occur with ionic interactions, particularly with the AN69 polyacrylonitrile membrane (6). The difficulty of collecting all the spent dialysis bath fluid during hemodialysis can be avoided by collecting timed interval samples during the hemodialysis session. This also makes it possible to evaluate clearance changes that might occur during the hemodialysis session

Because dialysis bath fluid is not routinely collected during hemodialysis therapy, Cl_D is usually estimated using the A-V difference method which is based on the Fick Equation:

$$Cl_D = Q_B \left[\frac{A - V}{A} \right] \qquad (3)$$

where the terms A, V, and Q_B are as shown in **Figure 1**. The terms in brackets describe an extraction ratio and, because plasma and blood concentrations are usually a fixed proportion of each other, either can be used to calculate this ratio. Unfortunately, this method of estimating CL_D is subject to error, primarily because plasma flow is used inappropriately in calculating plasma clearance and because of kinetic perturbations in drug distribution kinetics that occur during dialysis.

Whereas, it is appropriate to calculate CL_D as *blood clearance* by setting Q_D equal to measured blood flow when CL_R and CL_{NR} are also calculated as blood clearances, when CL_D is most often reported as *plasma clearance* and is usually estimated by setting Q equal to plasma flow (3, 4). However, this estimate of plasma clearance is only comparable to plasma clearances calculated for CL_R and CL_{NR} when the drug is totally excluded from erythrocytes. Otherwise, plasma clearance needs to be estimated using the *effective flow* through the dialyzer (Q_{Eff}), given as:

$$Q_{EFF} = Q_B \cdot B / P \qquad (4)$$

where B and P are the respective drug concentrations in blood and plasma. For example, many drugs partition preferentially into red blood cells and are fully or largely dialyzable from both plasma and erythrocytes. Consequently they will have Q_{Eff} values that are not less than but *exceed* measured blood flow (7). Assuming that all the drug in erythrocytes is dialyzable, an appropriate B/P ratio can be calculated from the drug's hematocrit (H) and erythrocyte/plasma partition coefficient (RBC/P) as follows:

$$B/P = (RBC/P)H + (1 - H) \qquad (5)$$

However, this assumption is unnecessary when CL_D is calculated by the recovery method and venous (V) as well as arterial (A) drug concentrations are included in the pharmacokinetic analysis. In this case, Q_{Eff} can also be estimated from a rearrangement of **Equation 3** and used to estimate the dialyzability of drug that partitions into erythrocytes (7).

Kinetic perturbations during hemodialysis:

Most hemodialysis studies are conducted assuming that drug distribution and elimination kinetics both remain unchanged during this procedure. However, Stec et al. (7) found that the intercompartmental clearance (CL_S) of N-acetylprocainamide (NAPA) between the central intravascular compartment and the slowly equilibrating peripheral compartment of a 3-compartment mammillary model decreased during hemodialysis to a maximum extent that averaged 77%. This reduction in CL_S was only apparent because the recovery method was used to estimate CL_D and the fall in A and V was greater than expected from the amount of drug recovered from the spent dialysate.

Because the fall in arterial blood concentrations was in part due to the change in drug distribution, it can be seen from **Equation 3** that the A-V difference method would have overestimated CL_D.

Of possible additional importance is that Nolin et al. (8) found that hepatic CYP3A4 metabolic activity, assessed with the erythromycin breath test, increases by 27% as soon as 2 hours after hemodialysis, apparently due to clearance of low molecular weight uremic toxins that act to inhibit this cytochrome. Should CL_{NR} actually begin to increase during hemodialysis, this also would lead to an over estimation of CL_D unless it is calculated by the recovery method.

Recommendations:

Because the clinical utility of pharmacokinetic studies in hemodialysis patients is critically dependent on the accuracy with which CL_D is estimated, we recommend adoption of the recovery method for these studies. It also is important that comparison with predialysis elimination clearance estimates be facilitated by the appropriate selection of either blood or plasma concentrations when calculating CL_D. The drug should be administered intravenously at a sufficient interval before hemodialysis is instituted so that predialysis distribution and elimination pharmacokinetics can be fully characterized. Reports should include the dialyzer model and the extent of ultrafiltration needed to compensate for interdialytic weight gain. In the ideal study, ultrafiltration would be minimized to limit the contribution of convection to estimates of CL_D. Finally, patients need to be studied long enough following dialysis to assess the extent of the postdialysis rebound in drug concentrations.

Results of pharmacokinetic studies in hemodialysis studies are used most commonly to estimate appropriate postdialysis supplementary doses of the drugs that are being administered to these patients. However, emergency hemodialysis may also be life-saving for patients who have received drug overdoses or have ingested toxic substances. In this latter setting, the beneficial effects of drug removal by hemodialysis are augmented by dialysis-associated reductions in CL_S that exaggerate the fall in plasma drug concentrations and consequently reduce the exposure of the brain, heart, and circulatory regulatory system to toxic drug concentrations. The fall in CL_S occurs not only during the dialysis period but is maintained for some time after hemodialysis, so has the effect of sequestering drug in pharmacologically inert somatic tissues (7). As a result, estimates of drug distribution volume made in these patients on the basis of the observed fall in plasma concentrations and measurements of drug recovered during dialysis will be much smaller than those obtained in non-dialyzed subjects (9). For this reason, hemodialysis may represent effective therapy for patients overdosed with drugs that are freely dialyzable but currently are not considered candidates for this intervention because of their large distribution volumes.

A continuing clinical problem is that pharmacokinetic results obtained with one dialyzer are generally not representative of the performance of other dialyzers. Thus, there is a critical need to characterize CL_D estimates made with one dialyzer in a way that results can be readily extrapolated to different dialyzer models. One approach could be based on *in vitro* studies in which the dialysis characteristics of a standard compound are compared across different dialyzers. For example, the contributions of dialyzer blood flow and permeability coefficient-surface area product (P·S) to CL_D were first analyzed by Renkin (10) using the following equation to calculate P·S values for a number of solutes from values of Q_B and CL_D obtained *in vitro* with a Kolff-Brigham dialyzer:

$$\mathbf{CL_D = Q_B \, (1 - e^{-P \cdot S/Q})} \tag{6}$$

Applying **Equation 6** to results from a study in which Gibson et al. (11) compared *in vitro* estimates of CL_D for procainamide (PA) and N-acetylprocainamide (NAPA) for 10 different dialyzers, it was found that the ratio of $P \cdot S_{PA}/P \cdot S_{NAPA}$ remained relatively constant, averaging 1.28 ± 0.23, similar to the ratio of their free water diffusion coefficients (12). For implementation of this approach, a suitable standard compound should have a molecular weight that is larger than that of urea (MW = 60 Da) and more typical of most dialyzable drugs so that its CL_D is substantially influenced by P·S rather than primarily determined by Q_B. Currently, all marketed dialyzers have clearance data for several solutes that routinely include *in vitro* estimates of their mass transfer area coefficient (KoA), analogous to P·S in **Equation 6**. Creatinine (MW = 113 Da), vitamin B12 (MW = 1,355 Da), and β2-microglobulin (MW = 11,800 Da) are all commonly used to characterize currently-available dialyzers and might be suitable standard compounds.

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Section 6: Drug Dosing in CRRT and Hybrid Dialysis Therapies
Bruce A. Mueller & Jan T. Kielstein

Optimal pharmacotherapy in critically ill patients with acute kidney injury (AKI) requiring renal replacement therapy (RRT) is essential. Sepsis is the most common contributing factor to the development of AKI,[1] yet antibiotic considerations are often an afterthought in the management of these patients. Several trials developed to determine the optimal continuous renal replacement therapy (CRRT) or hybrid RRT intensity have failed to increase antibiotic doses to account for the increased drug removal associated with the high-intensity CRRT arm.[2,3] The higher delivered clearance was associated with higher hypophosphatemia rates suggesting that the reported lack of superiority in higher CRRT doses may have been due to increased drug clearance and inadequate pharmacotherapy. These trials are an example of the larger problem: many intensivists, nephrologists and pharmacists making dosing decisions for a particularly vulnerable patient population are unaware of how newer forms of RRT can affect drug removal. Complicating the issue is the variability of how RRT is delivered in intensive care units (ICUs), and the lack of generalizability of the results of existing RRT pharmacokinetic trials.

What is known about Drug Dosing in CRRT and Hybrid RRT
CRRT is commonly used in the ICU because it provides a better tolerated form of solute removal for hemodynamically unstable patients. However, CRRT is not a standardized therapy, and practices vary widely. Several modes of therapy (convective, diffusive, or both), a variety of filter materials, and different effluent flow rates are used[4], all of which can influence drug removal. Despite the large variability in CRRT techniques, a review of published dialytic clearance studies found that less than 90% of studies specified the CRRT dose employed, and only 58% of CVVH studies specified whether pre- or post-dilution mode was used.[5] Two basic pharmacokinetic values necessary for interpretation of study results, volume of distribution (Vd) and clearance (CL), were specified in only 79% and 81% of studies, respectively. None of the reviewed studies contained the "ideal data set" formulated by the authors (Table 1).

Hybrid RRTs are gaining popularity in ICUs because they can be performed using standard hemodialysis machines, can be less expensive than CRRT to perform, and require less anticoagulation.[6,7] These therapies run at higher dialysate flow rates (usually 100-300 ml/min) than those used in CRRT, and treatment often lasts for 6-12 hours in duration, although more "continuous" forms of hybrid therapy have been reported.[8] Hybrid RRT techniques are not uniform, and many variations exist (Table 2).[7] Further complicating the issue is the lack of standard nomenclature, which can become confusing. Hybrid therapies include slow, low-efficiency dialysis (SLED), extended daily dialysis (EDD), continuous SLED (c-SLED), slow low-efficiency daily dialysis (SLEDD), slow low efficiency daily hemodiafiltration (SLEDD-f), NxStage Dialysis, and others, making literature searches and pharmacokinetic interpretation difficult. The intermittent nature of most hybrid RRTs can further complicate drug dosing, as higher amounts of drug may be needed during the therapy, while lower doses may be required during therapy downtime. To date, pharmacokinetic studies with only twelve drugs have been studied with hybrid RRTs (Table 3). A variant of CRRT, high volume hemofiltration (HVHF) has been advocated as sepsis therapy, but no pharmacokinetic studies have ever been published in HVHF.

Despite the dearth of information on drug dosing in CRRT and hybrid RRT, the FDA and EMEA do not currently mandate pharmacokinetic studies for these therapies. New draft FDA guidance language published in March 2010 does not mandate these studies either[9], so the lack of knowledge about appropriate drug dosing for critically ill patients requiring these therapies is likely to persist.

When evaluating drug dosages in patients receiving RRT, patient-related, drug-related, and RRT-related characteristics should be taken into account. Critically ill patients in AKI exhibit altered volumes of distribution, non-renal clearance[10], and serum protein concentrations compared to healthy volunteers with end-stage renal disease, and so drug dosing in healthy patients cannot simply be extended to include the critically ill population.[11,12] Patient body weight[13] and fluid status must also be considered. Obese patients may require larger drug doses, just as severely fluid overloaded patients

may require larger doses before RRT is started and fluid status is corrected. Drug-related factors influencing RRT removal include molecular weight, degree of protein binding, and volume of distribution. A drug is more likely to be removed by RRT if it has a smaller molecular weight,[14] has a small volume of distribution (often a cut off of <1L/kg is used), and is not substantially protein bound. A strong correlation exists between sieving coefficient and (100% - [% Protein Binding]) for most drugs. [15]

RRT parameters substantially influence drug clearance. The mode of therapy (diffusion, convection, or both) alone can be influential, as both therapies can remove small solutes, but convective therapies are superior at removing larger molecular weight solutes.[16,17] Drug clearance is affected by where replacement fluids are given, because this influences the drug concentration that travels through the filter. Mathematical calculations can account for this,[18-20] but published studies do not always specify this information.[5] Filter material and type also influence drug removal. The older, cuprophane filters did not remove larger drugs effectively in hemodialysis studies, while newer high-flux membranes can remove substantial amounts of drug.[21] Some degree of drug and other solute adsorption occurs with many dialysis membranes (particularly sulfonated polyacrylonitrile [AN69®] and polymethylmethacrylate [PMMA]), although it is difficult to quantify adsorption in both *in vitro* and *in vivo* studies.[22-24] Dialysis dose is one of the most influential factors of drug removal, with increased dialysate/ultrafiltration/effluent flow rates resulting in greater drug removal (although there may be something of a ceiling effect for diffusion-based therapies).[25]

Several methods have been suggested for calculating drug doses.
1) The first and most effective method would be to use therapeutic drug monitoring when possible. However, very few drugs have clinically useful (quick turnaround time, FDA/EMEA approved) assays available.
2) The most "evidence-based" method would be to consult current literature for studies of the drug in RRT. Unfortunately, this literature is limited and may not be generalizable across RRT settings and patient populations.
3) A commonly used method involves calculating a total creatinine clearance (CrCl) based on the addition of residual renal clearance and expected extracorporeal clearance, and using medication dosing guidelines specified for that total CrCl range.[26] Using this method, most drugs will fall in the CrCl 25-50 ml/min range. This method is useful, although it assumes that drugs only undergo glomerular filtration, not tubular secretion or reabsorption.
4) A fourth method starts with the dose and dosing interval for a patient with a GFR < 10 ml/min (anuric dose), and makes dosage adaptations based on the drug fraction expected to be removed by extracorporeal therapy.[27,28]
   i)   Maintenance dose = anuric dose/ $1-Fr_{EC}$
   ii) Dosing interval = anuric dosing interval X $(1-Fr_{EC})$
5) A fifth method starts with a normal dose (D_n), and reduces dose based on normal clearance (Cl_{normal}), non-renal clearance ($Cl_{non-renal}$), effluent rate (Qeff), & sieving coefficient (SC).[29]
   a.   Dose CVVH = $Dose_n$ X $[Cl_{non-renal} +(Q_{eff}$ X SC$)]/Cl_{normal}$

All methods fail to take each drug's pharmacodynamic profile into account. Pharmacodynamics, which examines how drug concentrations can be optimized to meet a therapeutic goal (i.e increase bacterial kill, reduce blood pressure, etc) is beginning to be better recognized as vital for patient outcomes. For example, pharmacodynamic targets have been identified for many antibiotics, and pharmacodynamic theory should be applied when making antibiotic dosing recommendations.[30,31] Finally, these equations may not be useful when making drug-dosing decisions with hybrid RRTs. Although the formulas might be able to suggest a reasonable dose, further consideration needs to be given to the timing of the drug dose in relation to the timing and duration of the hybrid RRT.

<u>What can be achieved with current knowledge?</u>
With the help of therapeutic drug monitoring, the current literature available, and the drug dosing methods outlined above, appropriate dosing recommendations can be formulated for most drugs, although confirmation with clinical trials is the only way to confirm that drug dosing is appropriate. For patients receiving CRRT, the 2007 publication "Drug Prescribing in Renal Failure" by Aronoff and colleagues gives recommendations for 475 drugs.[32] However, only 58 of the 475 drugs have ever been the subject of CRRT studies, and many were *in vitro* studies. For hybrid RRT, there is at least some human data available for 12 drugs (Table 2). One can probably extrapolate some of this knowledge to include other drugs (e.g. data about gentamicin dosing can probably be applied to tobramycin dosing), but the variability in hybrid techniques makes it difficult to apply recommendations published in one study to others.

With the state of current knowledge, efforts can be made to educate intensivists, nephrologists, and pharmacists about the intricacies of drug dosing in patients receiving CRRT/Hybrid RRT (as with the upcoming NEPHSAP) and the need for well-constructed drug-dosing studies that yield dosing recommendations that can be translated to patients receiving many types of RRT.

<u>Vision for what needs to be known to advance clinical practice</u>
An analysis of drug dosing in the published RRT intensity trials could help elucidate whether the reported lack of improvement in patient outcomes in the higher intensity RRT arms was due to inadequate antibiotic dosing. In order to optimize pharmacotherapy, further pharmacokinetic studies in RRT must be conducted. These trials should be expanded to include removal of all drugs used in critically ill patients that do not have a reliable and readily available measurable parameter of efficacy (e.g. blood glucose for insulin or blood pressure & heart rate for catecholamines). Pharmacokinetic studies in children are also urgently needed. Assessment of non-renal clearance changes in AKI and how RRT affects non-renal clearance must be performed. Finally, these pharmacokinetic studies must be linked with pharmacodynamic measures and patient outcomes to confirm appropriate therapy equates with improved patient outcomes.

Drug dosing recommendations on a mg/kg basis should be derived from these studies in adults and children instead of recommending a fixed dosage for everyone.[12] Special emphasis should be placed on patients with volume overload and obesity, common conditions in the ICU, but often used as exclusion criteria in pharmacokinetic trials.

Ideally, drug clearance studies should be done in conjunction with the development of new practices and technologies. Citrate anticoagulation has gained popularity, but the optimal (safe and efficacious) anticoagulation regimen for specific situations remains to be evaluated. The relationship between hemofilter age and drug clearance should also be assessed. The influence of newer high cut-off filters, high-volume hemofiltration, albumin dialysis, and other extracorporeal therapies (e.g. extracorporeal membrane oxygenation or invasive lung assist membrane ventilation) on drug clearance will need to quantified and used to make drug dosing recommendations.

New technologies that could greatly simplify drug dosing efforts include updated software that uses drug, RRT, and patient data to generate accurate initial drug dosing regimens, and automated pharmacy notification when CRRT goes down, perhaps with automatic dosing adjustments. The most helpful and large-scale recommendation by far would be worldwide RRT technology and dosing standardization in research and practice to reduce RRT variability as a source of error and increase generalizability of this research. In this case, pharmacokinetic trials could be conducted using one universal CRRT or hybrid RRT regimen, and results could be extrapolated widely.

Activism can play an important role in assisting with drug dosing as well. If the FDA and EMEA can be convinced to encourage drug manufacturers to conduct CRRT/Hybrid RRT pharmacokinetic trials for drugs commonly used in the ICU, much of the guesswork involved in dosing would be eliminated. Furthermore, it should be requested that package inserts of older drugs be updated to reflect contemporary RRT practices, as many resources recommend doses based on outdated RRT modes

(continuous arteriovenous hemofiltration), flow rates and filter types. With government and physician support, drug dosing can be made easier, and the safety of critically ill patients will be protected.

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Table 1. Ideal Data Set for RRT Pharmacokinetic Trials

Drug-related	Antibiotic assayed
	Specified target concentration
	Dose recommendation
Patient-related	Age
	Weight
	Severity of illness
	Number of patients in study
	Residual renal function
	Hepatic dysfunction
Basic pharmacokinetics	Volume of distribution (Vd)
	Total, CRRT, and non-CRRT clearances
	Protein binding/serum albumin
CRRT clearance	Membrane type/surface area
	Mode of CRRT
	Pre-filter/post-filter fluid replacement (if applicable)
	If pre-filter replacement: Hct, predilution replacement rate
	Sieving/saturation coefficients
	Dialysate/ ultrafiltration effluent rates
	Blood flow rates

Adapted from: Li AM, Gomersall CD, Choi G, Tian Q, Joynt GM, Lipman JJ. A systematic review of antibiotic dosing regimens for septic patients receiving continuous renal replacement therapy: do current studies supply sufficient data? Antimicrob Chemother 2009;64(5):929-37.

Table 2. Studies of sustained low-efficiency dialysis and extended nocturnal dialysis for treatment of patients with renal failure in the intensive care unit.

Author	Dialysis machine	Blood/dialysate flow (ml/min)	Prescribed treatment time (h)	Nocturnal treatment
Fiaccadori et al.[24]	AK200® Ultra	200/100	8–9	No
Kielstein et al.[21]	Genius®	200/100	12	Yes
Kielstein et al.[43]	Genius®	150–200/150–200	8	Yes
Kumar et al.[18]	2008H®a	200/300	6–8	No
Lonnemann et al.[19]	Genius®	70/70	18	Not reported
Marshall et al.[20]	2008H®a	200/100	12	Yes
Marshall et al.[22]	2008H®a	200/100	12	Not reported
Marshall et al.[22]	4008S ArRT-Plus	250–350/200	8	No
Morgera et al.[33]	Genius®	180–200/180–200	4–6	No
Naka et al.[51]	Not reported	100/200	6–8	Not reported
Ratanarat et al.[25]	Not reported	200–250/67–150	6–12	Not reported
Schlaeper et al.[17]	2008H®a	100–200/100–300	8–24	Yes

aModified for SLED treatment mode.

From: Fliser, D.F. and Kielstein J.T. Technology insight: treatment of renal failure in the intensive care unit with extended dialysis. Nat. Clin Pract Nephrol 2006;2:32-9.

Table 3. Published pharmacokinetic studies conducted in patients receiving SLED

Drug	Year	Lead Author	n	SLED duration (hr)	Qb (ml/min)	Qd (ml/min)	Filter type & Surface area (m^2)	Dosing Recommendation
Ampicillin/ sulbactam (1)	2009	J. Kielstein	1	7.5	180	180	PS, 1.3 m^2	None provided
Anidulafungin (2)	2009	O. Burkhardt	1	8	180	180	PS, 1.3 m^2	No dose adjustment necessary
Daptomycin (3)	2008	O. Burkhardt	1	12	200	100	PS, 1.3 m^2	None provided
Daptomycin (4)	2010	J. Kielstein	10	8	160	160	PS, 1.3 m^2	6 mg/kg daily, 8 hrs prior to SLED
Ertapenem (5)	2009	O. Burkhardt	6	8	160	160	PS, 1.3 m^2	1 gram IV daily
Gentamicin (6)	2003	H. Manley	8	8	200	300	PS, 0.5 m^2	2.0-2.5 mg/kg post SLED*
Levofloxacin (7)	2006	D. Czock	5	8	160	160	PS, 1.3 m^2	None provided- give post SLED
Linezolid (8)	2004	E. Fiaccadori	5	8-9	200	100	PS, 1.6, 1.4 m^2†	None provided- give post SLED
Linezolid (9)	2010	S. Swoboda	10	12-24	110-150	110-150	PS, 1.3 m^2	TDM in patients with liver disease
Meropenem (10)	2005	J. Kielstein	10	8	160	160	PS, 1.3 m^2	0.5-1 gm q8 hrs, depends on weight, illness severity
Moxifloxacin (7)	2006	D. Czock	10	8	160	160	PS, 1.3 m^2	400 mg IV daily post SLED
Vancomycin (11)	2004	J. Ahern	11	24	200	100	PS 0.7, 0.9 m^2†	15 mg/kg load, TDM
Vancomycin (10)	2005	J. Kielstein	10	8	160	160	PS, 1.3 m^2	20-25 mg/kg load, TDM
Vancomycin (12)	2009	L. Golestaneh	10	8	150-200	100-200	PS, 0.7 m^2	TDM
Voriconzole (13)	2010	O. Burkhardt	4	8	180	180	PS, 1.3 m^2	Avoid IV administration due to SBECD accumulation

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Section 7: Drug Removal by Peritoneal Dialysis (see refs. 1-6)
Thomas Golper and Franz Schaefer

One major principle of dialytic clearance answers quickly the role of peritoneal dialysis in the removal of drugs: **clearance can never exceed dialysate flow rate**. If dialysate is 100% saturated with the solute in question, then the dialytic clearance is equal to the dialysate flow rate. This principle is used routinely in PD regarding the solutes urea and creatinine, two unbound (not bound to circulating proteins) solutes generally equal to or considerably smaller in molecular size and weight to most drugs. The dialysate concentration (D) to the plasma concentration (P) ratio is a standard tool in the measurement of PD dosing. Clearance is the D/P times the effluent volume per unit time. The D/P ratio will vary by the peritoneal membrane's intrinsic transport status, defined by the D/P for creatinine at four hours. This standard definition of the ratio at 4 hours is helpful conceptually. However, in practice exchanges vary in duration so that PD dosing is assessed by the D/P creatinine (or D/P urea) determined from the pooled effluent dialysate over a precise 24 hours. From this a daily clearance is determined, then multiplied by 7 to calculate a weekly clearance. Urea clearance is normalized to total body water volume (V) and creatinine clearance is normalized to 1.7 meter^2 of body surface area.

One would utilize a similar strategy to calculate drug clearance by PD. Only unbound drug is available to diffuse into dialysate. A very small and negligible amount of protein bound drug would enter the dialysate through convection. Thus, the drug dialysate concentration (D) will be less than that of the plasma concentration (P) for any protein bound drug, regardless of the transplant properties of the membrane. If the drug is unbound and freely diffusible like urea and creatinine, the drug clearance could never exceed dialysate flow rate.

Urea is the ideal marker molecule for a reference point because it transports quickly due to its size and lack of protein binding. Most patients on peritoneal dialysis have a dialytic weekly Kt/V of < 2.0 and V of < 40 liters. The urea clearance in this example is just under 15 mL/min. It is very unlikely that any drug clearance would exceed 15 ml/min. It could, of course if the drug is unbound, has a small molecular size, and the weekly urea Kt/V was ≥2.0, which could be achieved by very aggressive peritoneal dialysis dosing. One might employ such a strategy for a poisoning in an attempt to remove the poison by PD. However, most typical PD dosing is in the range of a urea clearance of about 15 mL/min or lower. The molecular size of creatinine is larger than that of urea, and this slows down its diffusion and clearance, such that for a typical patient the clearance of creatinine is perhaps 3/4ths that of urea. Since most drugs are larger than creatinine, their clearance is even less. So a drug's clearance by PD is very likely to be 10 mL/min or lower.

Many studies performed in the 1970's and 1980's showed that drug clearances by PD were in this very low range, and concluded that PD is not a major factor in dialytic drug removal. This is particularly true over short time periods. Over days, this continuous low clearance can lead to the slow removal of a drug which is infrequently dosed.

Peritoneal dialysis might indirectly affect drug clearance by enhancing or decreasing non-dialytic clearances. This would depend on the mechanism of the non- dialytic clearance and would be unique to that drug. This also is quantifiably negligible.

Drug Administration by Peritoneal Dialysis

In patients with established peritoneal dialysis, the access to the peritoneal cavity provides an opportunity to deliver drugs both locally and systemically.

The efficacy of transperitoneal drug resorption depends on the dialysate volume in which the drug is diluted, the dialysate to plasma concentration gradient, the molecular size and electrochemical properties of the compound, the exposure time and the peritoneal perfusion rate (7).

Intraperitoneal drug administration is well accepted for the antibiotic therapy of peritoneal dialysis-associated peritonitis and other infections (8). The intraperitoneal route has also been proposed to administer hormones such as insulin, erythropoietin, growth hormone and calcitriol.

Intraperitoneal therapy appears attractive but has several potential technical pitfalls that require attention. These include the solubility and stability of the compounds in PD fluid (9,10). Drug stability and solubility may depend on the composition of PD fluids, which vary in buffer, pH and other components. Also, co-administration of more than one compound can lead to chemical interactions and changes in solubility.

Antibiotics

Bacterial peritonitis is a potentially life-threatening disease which requires rapid, efficacious therapy. Intraperitoneal instillation of antibiotics immediately establishes high bactericidal concentrations at the site of infection. In addition, absorption from the peritoneal cavity leads to therapeutic blood concentrations. The drug doses delivered to the peritoneal space required to achieve adequate blood levels have been established in pharmacokinetic studies for most currently used antibiotics (11,12). Intraperitoneal administration has become the standard application modality in the treatment of peritonitis for most antibiotics.

For drugs with good peritoneal resorption and a long pharmacological and/or biological half-life, **intermittent dosing** is an option. Following systemic resorption, the body is used as a reservoir for continuous back-diffusion of the antibiotic into the peritoneal cavity. Ideally, dialysate concentrations at the end of the antibiotic-free dwell will exceed the minimum inhibitory concentration of the infecting organism (12-14).

Administration intervals will depend on the half-life of the drug, which is mainly determined by protein binding and residual renal and extrarenal metabolic clearance. Long-standing experience with intermittent antibiotic administration exists for the glycopeptides vancomycin and teicoplanin, which can be administered at 5- to 7-day intervals, as well as for aminoglycosides and cephalosporins suitable for once daily dosing (8,12,14,15).

While the concept of intermittent antibiotic administration appears intriguing due to its practicality and cost efficiency, the efficacy and safety of intermittent dosing is affected by several factors. Most importantly, the dialysate flow rate strongly affects both the resorption and the elimination of the drug (13). In patients treated by automated PD (APD) with frequent short dialysis cycles, exposure to PD fluid with a given antibiotic concentration over several cycles may result in greater cumulative resorption and higher plasma levels as compared to antibiotic loading in a single extended dwell period in patients on continuous ambulatory PD (CAPD). Conversely, the higher dialysate flow and small molecule clearance achieved with APD regimens may lead to a greater peritoneal clearance of antibiotic in the periods between dosing (12).

Since most pharmacokinetic studies establishing peritoneal antibiotic doses have used 4- to 8-hour loading periods, it has been recommended to perform antibiotic loading by an extended cycle both in CAPD and in APD patients (8). For intermittent maintenance dosing a long nighttime dwell should be used in CAPD and a long daytime dwell in APD patients.

In clinical practice intermittent antibiotic dosing has not been unequivocally successful in eradicating bacterial growth, partially questioning the concept of antibiotic back diffusion into the peritoneal cavity (15-18). Transperitoneal drug movement may be less effective in the post-acute phase of peritoneal infection when inflammation-related capillary hyperperfusion subsides. Also, short dwell times in APD patients may prevent accumulation of antibiotic in the peritoneal cavity to concentrations exceeding the minimal inhibitory concentrations. The clinical efficacy of intermittent dosing may also depend on post-antibiotic properties, as described for aminoglycosides but not cephalosporins.

Monitoring of drug blood levels has been advocated in patients receiving intraperitoneal antibiotics who are at increased risk for under- and overdosing, i.e. those with significant residual renal function and those on intense APD schedules (8,15). Monitoring of dialysate concentrations may provide even more relevant information.

Hormones

In patients receiving chronic peritoneal dialysis, the intraperitoneal route has been explored as an alternative to subcutaneous injections in the long-term administration of polypeptide hormones such as insulin in patients with diabetic nephropathy, epoietin and growth hormone. Intraperitoneal treatment experience is also available for the active vitamin D analogues calcitriol and 22-oxa-calcitriol. Adsorption to plastic bags and tubing appears to be minimal for epoietin and growth hormone (<7%), whereas 35-40% adherence to PD materials has been observed with calcitriol and 20-65 % for insulin (19-22).

Insulin is well resorbed from the peritoneal cavity. Primary intraperitoneal administration of insulin in diabetic patients on PD has been advocated as it might result in a more steady resorption and a more physiological plasma insulin and blood glucose profile (23,24). The limited body of evidence published to date suggests equivalent or superior blood glucose control with the intraperitoneal as compared to the subcutaneous route (25,26). Intraperitoneal insulin dose requirements are simular or reduced compared to the subcutaneous route if insulin is administered into an empty peritoneal cavity (26). Hypoglycemic episodes are less frequent but diabetes-associated dyslipidemia is more common with subcutaneous administration (25,26). Whereas peritonitis incidence does not appear to differ consistently between the administration modes, subcapsular hepatic steatosis has been described anecdotally in diabetics receiving insulin intraperitoneally (27). More importantly, concern has been raised that insulin, due to its growth factor properties, might stimulate neoangiogenesis in the peritoneum. This concern, together with the relative inconvenience of intraperitoneal administration, has led to the clinical practice recommendations in favour of the subcutaneous route in diabetic patients on CPD.

Efficient transperitoneal resorption has been demonstrated for the recombinant *erythropoietins* alpha-epoietin, ß-epoietin and alpha-darbepoietin (28-35). Bioavailability is strongly dependent on the degree of dilution in PD fluid and exposure time, with blood concentrations peaking after 12-14 hours of exposure. Studies using a small volume of PD fluid to instill epoietin compounds during an extended dwell (e.g. during daytime in patients on APD) observed similar bioavailability, pharmacodynamics and dose requirements as with subcutaneous administration (28,30,33,34). However, the variability of dose requirements appears to be greater with the intraperitoneal route.

A single uncontrolled prospective study has evaluated the efficacy of intraperitoneal recombinant *growth hormone* in 9 children on chronic PD (35). Good bioavailability was demonstrated, with peak plasma levels reached 4 hours after administration. The growth stimulating effect within 2 years of therapy was comparable to the effect typically seen with subcutaneous growth hormone administration.

The chronic intraperitoneal treatment approach has received particular attention in the peptide hormone treatment of children, in whom the avoidance of painful subcutaneous injections may contribute significantly to quality of life. On the other hand, regular injections into PD bags are associated with a slight increase in peritonitis risk, and modern pen device technology has reduced the hastle of subcutaneous injections. Consequently, very few centers are currently using the intraperitoneal route to administer epoietin or growth hormone.

Intraperitoneal administration of the injectable formulation of calcitriol has been proposed in chronic PD patients. Calcitriol is rapidly resorbed when injected intraperitoneally, with a bioavailability comparable to oral and 50% lower than achieved by intravenous administration (37-41). Intraperitoneal 'pulse therapy', i.e. intermittent administration 2-3 times weekly, is significantly more effective in reducing PTH levels than a respective oral pulse treatment protocol (39,41). Despite - or even because of - its high efficacy, the appeal of intraperitoneal pulse therapy has diminished in recent years in view of cardiovascular vascular risks associated with high dose vitamin D treatment.

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# Section 8: Drug dosing in patients with multiple organ dysfunction

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Background

Critically ill patients frequently develop multi-organ dysfunction a devastating complication associated with a very high mortality rate of 50-80%.. The clinical presentation of MSOF / MODS has evolved over the last 30 years. Although most cases of MODS occur secondary to shock, sepsis, and severe trauma a multiplicity of other risk factors have been identified. Initially post injury MSOF / MODS was thought to be an overwhelming, uncontrolled sepsis response. Over 90% of patients who develop MSOF / MODS have early respiratory dysfunction. Cardiac dysfunction often is observed within the next day, followed by hepatic dysfunction within 4-6 days and renal dysfunction in 5-7 days (Fig 1). The heterogeneous patient population and lack of agreement on a single standardized scoring system limit the tracking of progress in the management of MODS. The incidence and the magnitude of MODS has decreased over the last 20 years, but it still remains a significant issue. A recent prospective study reported a 17% incidence of MODS and 45% mortality rate among more than 7,000 patients from 79 ICUs. [Intensive Care Med 2005;31:927–33] Thus there remains a great need to improve our diagnostic and therapeutic approaches if we hope to be able to improve patient outcomes. Patients with MODS invariably require multiple drugs for management. In most instances drug dosing is based on knowledge of drug disposition derived from

studies in subjects with varying severity of disease. Unfortunately, there are large gaps in knowledge of drug metabolism and disposition in patients with multi organ dysfunction and there may be significant risk for under or overdosing patients. Drug dosing strategies in patients with multiorgan failure need to consider several variables that influence drug handling. This section provides a frame work for a systematic appraisal of the current knowledge of drug dosing in MODS, provides recommendations for management of patients, and outlines areas for future research.
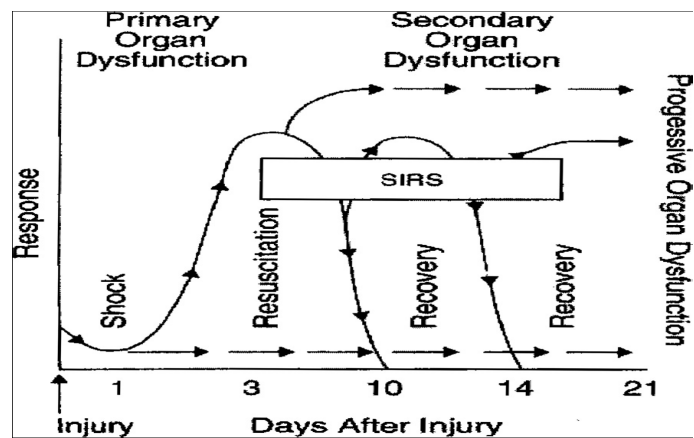
Scope of Work

Patients with multiorgan failure comprise several overlapping conditions. In general these can be considered in three broad categories based on the acuity of illness and underlying co-morbidities: **Multiple Organ Dysfunction Syndrome – Acute** i.e., the initial insult leads to alterations in the function of multiple organ systems in acutely ill patients; **Multiple System Organ Failure – Acute on Chronic disease** i.e., Altered / worsening organ function or the development of a new organ dysfunction in the patient with pre-existing co-morbidites; **Multiple Organ Dysfunction Syndrome – Chronic** *Clinical practice guidelines rarely account for patients with multiple chronic conditions* (JAMA 2010;303:1303-4)

Methodology

Medline database from January 2000 through March 2010 for literature with the medical subject headings: 'acute renal failure', 'acute kidney injury', 'chronic kidney disease', 'MODS', 'MSOF, 'hepatorenal syndrome', 'liver failure', 'cirrhosis', 'heart failure', 'intensive care' and 'critically ill'. All searches were limited to studies of human subjects and were conducted as advanced searches cross-referenced with 'pharmacokinetics' as well as 'drug dosing'. The searches produced a total of 6,456 citations. Each search was reviewed by

a panel of experts to ascertain its relevance to one of the three focuses of the group as outlined above.

What is known
Organ Perfusion is altered in MODS
Although cardiac output is typically increased in MODS, it is not evenly distributed due to regional differences in autoregulation of blood flow. Renal blood flow may initially be increased as a result. While other organs, i.e., the gut may be hypoperfused despite adequate indexes of global perfusion. In this regard, the hepatosplanchnic circulation is highly vulnerable to a reduction in tissue perfusion because it has limited ability to autoregulate.

Changes in renal function span spectrum from augmented to dramatic reducations
Hyperfiltration, creatinine clearances > 140 mL/min or more may be as problematic as a decline in renal function It is often been documented early in the course of MODS and especially in those with burns or trauma and can lead to the use of inappropriately low doses of medication can lead to treatment failure and even death. [Udy AA et al Clin Pharmacokinetics 2010;49:1-16] Hypofiltration may be especially challenging to quantify in those with changing function. [VerbeeckRK Musuamba FT Eur J Clin Pharmacol 2009;65:757-73] Patients receiving RRT add additional complexity particularly when the therapy is intermittently interrupted.

Renal function quantification is often difficult
Estimation or measurement of GFR does not provide an accurate measure of the contribution of kidney to renal excretion of all drugs: especially those that are extensively secreted, and /or metabolized in the kidney or other organs. Several new quantitative techniques and assessment protocols have been developed and utilized in patients with "stable" CKD, liver disease, and several other conditions but rarely has one of these approaches been used in MODS patients. [Tett SE et al Clin Pharmacokinet 2003; 42 (14): 1193-1211,] The potential benefits of these methods are an improvement in dosage individualization of renally eliminated drugs and identification of the mechanisms responsible for renal disease and nephrotoxic injury.Although both methods have been validated there has been no subsequent published data regarding their application neither in patients with chronic conditions nor in those who are critically Ill with MODS.

Renal function declines also can alter drug metabolism
Critically ill patients with early onset AKI have a higher residual non-renal clearance of some drugs, imipenem, vancomycin and some beta lactams, than patients with CKD who have a similar creatinine clearance. This may be the result of less exposure to or accumulation of uremic waste-products that may alter hepatic, gut, or intra kidney metabolism. Drug administration early in this clinical situation based on data from CKD patients would result in the attainment of lower than desired and possibly sub-therapeutic serum concentrations. As AKI persists, beyond 5-7 days, the existing evidence suggests that the non-renal clearance declines for the drugs identified above to values similar to what has been observed in stable CKD patients with comparable degrees of renal function.

Liver Function plays an important role and needs to be quantified
Liver dysfunction during critical illness is associated with a poor outcome that is independent of other organ dysfunctions; critical risk factors include; shock, sepsis, mechanical ventilation with positive end-expiratory pressure, and major surgery. Diagnosis of hepatic dysfunction in its early stages may be difficult due to insensitivity of standard liver function tests and severity scoring tools. Most organ failure scoring systems grade the severity of hepatic dysfunction based on serum bilirubin and/or transaminases and there may be minimal association between these measures and drug metabolizing capacity.

Multiple clinical investigators have devised genotyping procedures as well as "cocktail" approaches to characterize the phenotypic activity of several drug metabolizing enzymes. These approaches have yielded clear evidence of the dramatic effect of liver disease and other systemic diseases such as CKD and diabetes as well as obesity on drug metabolism. There is no evidence at this time of the utility of these technologies to assist in drug dosage regimen design for patients with AKI or MODS.

What is known regarding pharmacokinetics of drugs and dosage guidelines for their use in critically Ill Patients?

Erratic gastrointestinal absorption due to gut hypoperfusion, gut barrier injury, or postoperative ileus is likely. Variations in the extracellular fluid volume as a response to trauma, the resuscitation fluid load and/or as a consequence of continuous renal replacement therapy are often dramatic. In fact the distribution volume of many drugs has been noted to be increased by 25-50% in critically ill patients' esp. those with AKI. Altered drug metabolism due to the systemic inflammatory response or liver and or kidney dysfunction as a component of MODS has been noted for a small cadre of medications. The adverse effects of drug-drug pharmacokinetic and or pharmacodynamic interactions as the result of polypharmacy must be minimized.

Thus in critically ill patients, several drugs may need dosing regimens significantly different from those suggested in clinically stable patients with similar chronic diseases. During the early stages of MODS, patients will likely need higher initial doses and more frequent administration of maintenance doses. CAUTION should be applied when using nephrotoxic or hepatotoxic drugs, with a special emphasis on: changes in renal and metabolic clearance, the impact of renal replacement therapies, and the patient's fluid volume status.

Gaps in Knowledge

- ✓ What index of renal, liver, or other organ function should one use as a guide for drug dosage regimen individualization / adjustment in patients with MODS? This will require an assessment in Adults, Pediatrics, Geriatrics, and those with other co-morbid conditions such as, Inflammatory conditions, Obesity, Burns, and Trauma
- ✓ How does one individualize drug dosage regimens and evaluate its appropriateness when organ function is changing rapidly?
- ✓ What is the role of systemic illnesses such as cancer, diabetes, sepsis, etc and the therapies used to manage them on drug disposition or dynamics in MODS?
- ✓ Do pre-clinical models of MODS or co-morbid chronic diseases predict the human condition?
- ✓ What is the role of "in silico" modeling ?
- ✓ Is therapeutic drug monitoring and PK modeling an effective means to optimize drug therapy outcomes?
- ✓ How can industry and regulatory agencies encourage characterization of the influence of more than one acute or chronic disease / condition on the disposition of a drug?
- ✓ How can this pharmacokinetic and pharmacodynamic information be used to design clinically relevant drug dosing recommendations for patients with MODS?

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