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Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO)

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Drug dosage adjustment for patients with acute or chronic kidney disease is an accepted standard of practice. The challenge is how to accurately estimate a patient's kidney function in both acute and chronic kidney disease and determine the influence of renal replacement therapies on drug disposition. Kidney Disease: Improving Global Outcomes (KDIGO) held a conference to investigate these issues and propose recommendations for practitioners, researchers, and those involved in the drug development and regulatory arenas. The conference attendees discussed the major challenges facing drug dosage adjustment for patients with kidney disease. In particular, although glomerular filtration rate is the metric used to guide dose adjustment, kidney disease does affect nonrenal clearances, and this is not adequately considered in most pharmacokinetic studies. There are also inadequate studies in patients receiving all forms of renal replacement therapy and in the pediatric population. The conference generated 37 recommendations for clinical practice, 32 recommendations for future research directions, and 24 recommendations for regulatory agencies (US Food and Drug Administration and European Medicines Agency) to enhance the quality of pharmacokinetic and pharmacodynamic information available to clinicians. The KDIGO Conference highlighted the gaps and focused on crafting paths to the future that will stimulate research and improve the global outcomes of patients with acute and chronic kidney disease.

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In May 2010, Kidney Disease: Improving Global Outcomes (KDIGO) convened a Controversies Conference titled 'Drug Prescribing in Kidney Disease: Initiative for Improved Dosing'. The conference, attended by 50 international experts, including representatives from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), was designed to explore our understanding of drug disposition in patients with acute kidney injury (AKI) and chronic kidney disease (CKD), and to propose recommendations for the optimization of pharmacotherapy in the most common clinical practice settings. The plenary session presentations were followed by breakout group discussions to address four specific issues that the conference planning committee considered to be of central importance: (1) effects of impaired kidney function on drug disposition and response, (2) patient assessment for drug dosing, (3) calculating drug doses for patients with AKI and CKD, and (4) drug removal by intermittent and continuous renal replacement therapies. The breakout group deliberations were reported to the entire group and a consensus-building process led to the clinical practice, research, and regulatory

recommendations from the conference attendees, which is the substance of this report. The conference agenda, selected presentations, and abstracts of the meeting are available on the KDIGO website (http://www.kdigo.org/meetings_events/drug_Prescribing_in_KD-Initiative_for_Improved_Dosing.php).

AKI and CKD can affect multiple organ systems and these physiological changes have been associated with profound alterations in the pharmacokinetics (PK) and the pharmacodynamics (PD) of many drugs.[1,2] Clinicians must assess kidney function and consider how the kidney function-associated changes in the disposition of drugs and their active or toxic metabolites will impact the drug therapy needs of individual patients.

The number of patients with AKI and CKD has increased dramatically in the past 10 years.[3,4] Advances in the treatment of disease in general have permitted patients to live longer and many of them develop decreased kidney function over time. Indeed, kidney function decreases with age, and older patients constitute the most rapidly expanding patient group with CKD. The introduction of many novel renal replacement therapies (RRTs) for treating AKI and CKD mandate an understanding of their influence on drug disposition and response. New hemodialysis (HD) membranes and devices, intermittent, automated and continuous peritoneal dialysis, and the development of continuous RRTs necessitate evaluations and in some cases reevaluations of drug transport across biological and artificial membranes.

Pharmacotherapy is now widely utilized to manage chronic conditions by primary care providers, and intensivists are frequently faced with the need to individualize the acute care medication needs while not upsetting the patient's delicate therapeutic balance. CKD patients have poorer health outcomes than patients with normal renal function and the nonoptimization of drug therapy may be one of the contributing factors that could be addressed if more data were available and emphasis was focused on its incorporation into patient care plans.

THE CONTROVERSY

The pharmacokinetic era that began in the 1960s provided many methods to quantify drug concentrations and tools to characterize the influence of multiple factors including kidney function on the disposition of drugs.[5,6] In subsequent years the pharmaceutical industry began to investigate the relationship of kidney function and the PK as well as the PD of the drugs they had in development. There was no regulatory agency guidance during the 1970s to early 1990s that provided a framework for when investigations should be conducted and with what degree of rigor. Thus, much of the information on the PK/PD of drugs in patients with renal insufficiency was the result of clinician-initiated postmarketing studies. These studies often employed small sample sizes and resulted in the publication of frequently inconsistent or in some cases even conflicting recommendations regarding the need for drug dosage regimen adjustment. Comprehensive evaluations of clinical PK and PD of drugs and the resultant drug dosage regimen adjustment recommendations for CKD patients has been the topic of hundreds of articles in the past two decades and has become a standard feature in almost all clinical pharmacology and therapeutics textbooks. This wealth of data and expert opinion has fueled controversy regarding almost every step in the process of drug therapy individualization. The critical questions range from: What patient assessment considerations should be factored into the decision-making process? What is the most accurate and reliable index of 'kidney function' for drug dosing? What are the determinates of the desired therapeutic end points that guide therapy, the significance of risk associated with the accumulation of excessive drug and/or metabolite concentrations, and the degree of impact of AKI or CKD on the PK or PD of a drug? How to make pharmaceutical company-derived drug PK and PD readily available to clinicians? What is the predictive performance of the various methodologies to calculate the desired dosage regimen? What are the essential criteria that need to be met to reliably quantify the influence of RRTs on a drug PK and PD, which mathematical methods should be used to individualize drug therapy for those receiving RRTs, and finally what educational efforts should be developed to enhance drug prescribing for patients with AKI and CKD?

ASSESSMENT OF KIDNEY FUNCTION

The standard measure of kidney function for decades has been the glomerular filtration rate (GFR).[7] The measurement of GFR can be accomplished using many exogenous substances. Urinary clearance of inulin, which is the gold standard, is rarely performed except for research purposes because of the limited availability of the substance and the labor intensity of the procedure and the assay.[8] Modifications to this procedure include the use of other exogenous agents such as iothalamate, iohexol, and (99 m)Tc/c-diethylenetriamine pentaacetic acid, and plasma clearance to replace the need for urine collections. These are all more commonly available and utilized, but have limitations.[9] For example, some of the markers are not completely eliminated by GFR but are secreted by the tubules. Calculation of plasma clearance requires extrapolation of the area under the curve (AUC), which is often unreliable in those with the greatest degree of kidney function impairment or those with extensive edema, and even with these markers, the procedures are cumbersome and subject to error unless done under careful controlled conditions.[10] The determination of GFR based on the administration of exogenous substances is not practical for routine individual drug dose calculations as they are not timely and not uniformly available.

The determination of GFR utilizing an endogenous substance has therefore been based on the urinary clearance of creatinine (CL_{cr}) derived from a 24 h urine collection.[7,11,12] This method is of limited clinical value because of frequent urine collection errors (even when relatively short urine

Table 1 | Mathematical approaches to estimate GFR that have been proposed to guide drug dosage adjustment

Equations	Units	Reference
Cockcroft and Gault CL_{cr}=(140−age (years) × weight (kg) × 0.85 *[female]*)/(Scr (mg/dl) × 72)	ml/min	13
MDRD (four-variable) Study equation $GFR=186.3 \cdot Scr^{-1.154} \cdot Age^{-0.203} 1.212$ [*black*] · 0.742 [*female*]	ml/min per 1.73 m^2	19
MDRD (four-variable) Study equation for IDMS serum creatinine $GFR=175.6 \cdot Scr^{-1.154} \cdot Age^{-0.203} 1.212$ [*black*] · 0.742 [*female*]	ml/min per 1.73 m^2	19
CKD-EPI[a] $GFR_{\alpha}=141 \cdot \min(Scr/\kappa,1)^{\alpha} \cdot \max(Scr/\kappa,1)^{-1.209} \cdot 0.993^{Age} \cdot 1.159$ [*black*] · 1.018 [*female*]	ml/min per 1.73 m^2	17

Abbreviations: CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; CL_{cr}, creatinine clearance; GFR, glomerular filtration rate; IDMS, isotope dilution mass spectroscopy; MDRD, Modification of Diet in Renal Disease.
[a]Here, 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.

collection durations of 2–12 h are utilized), analytical interference with the serum or urine creatinine assay as the result of concomitant diseases and drug therapies, and the associated delay in the reporting of the results.[8] Therefore, GFR is predominantly estimated in clinical practice from the measurement of endogenous substances such as serum creatinine (S_{cr}) and then combined with patient factors to estimate the GFR using estimating equations.[13–19] The advantage of this method is that the results are available for routine clinical practice, and that for the majority of people, estimated GFR provides an unbiased assessment of measured GFR.[17] Estimating equations are on average more accurate than measured creatinine clearance, given the errors in urine collection (Table 1).[17]

There are limitations to S_{cr}. In particular, because S_{cr} is generated from muscle mass and diet, individuals at the extremes of these factors (for example, amputee or conversely body builders, or those on a vegan diet) will have substantially different values of creatinine than expected, and therefore the estimated GFR will be higher or lower than the true GFR for an individual patient and imprecision of the equation overall.[20] This limitation of S_{cr} is regardless of which equation is used to estimate GFR, and cannot be overcome by an adjustment of the equation.[9]

Another limitation of S_{cr} is the variability in S_{cr} assays. The variation in the assays led to differences in reported S_{cr} values among laboratories as well as within laboratories over time, even when the same methods are used.[21] This variation leads to differences in estimated GFR values when these different assays are used. In 2005, the National Institute of Standards and Technologies released materials that are traceable to the certified reference materials for creatinine whose value was assigned using isotope dilution mass spectroscopy (IDMS).[22,23] It is now estimated that the majority of laboratories currently report creatinine values traceable to this reference method. It is not possible to determine the precise relationship between IDMS-standardized S_{cr} values and prior values because of the substantial variability even within the same method in their creatinine results. For example, creatinine measurements by the various Jaffe methods yield S_{cr} values that are 5–10% higher on average than determinations by the IDMS technique. Although some have proposed a singular 'correction' value approach when using equations that were derived from creatinine measured by the Jaffe method (S_{Cr} (IDMS) = 0.92 × S_{Cr} (Jaffe)), this is not a valid approach given the wide variability among and within methods described above. Recently, some have proposed and developed a methodology to convert IDMS-traceable S_{cr} values into non-IDMS-calibrated S_{cr} values for application in CL_{cr} calculations to determine drug dosage adjustments.[24] This institution-specific methodology avoids the inappropriate 'generalization' of one correction factor to many patient care settings but it may not be feasible for most clinicians to utilize in their practice. The use of IDMS creatinine assays will likely lead to less variation in kidney function estimates and theoretically more consistent drug dosing recommendations across institutions and clinical settings. However, the variation in the creatinine assays before the availability of standardized creatinine assays does effect the relationships from PK/PD drug studies of the past, and therefore interpretation of product label drug dosing recommendations in the current era.[25] Estimated GFR based on current creatinine assays are likely to yield different drug dosage recommendations from those intended by the original study even if the same estimating equation is used because of this change in analytical methodology. It is not possible or practical to repeat all of the PK studies with standardized creatinine, and therefore as discussed in the section below 'drug dosing consideration for patients with CKD', it is still reasonable to use drug dosing adjustments in the product labeling.

Historically, the most frequently clinically used equation to estimate GFR has been the Cockcroft and Gault (CG) equation[13] (see Table 1). This equation provides an estimate of measured CL_{cr} and has been widely used as an estimate of GFR as well, despite the fact that creatinine also undergoes tubular secretion. The CG equation is reported in units not adjusted for body surface area, which is appropriate for drug dosage adjustment. The CG equation has been shown to overestimate GFR with the use of standardized creatinine assays.[26] Many have considered that an advantage of the CG equation for individual drug dose adjustment is that the body weight is considered; however, this has not been validated. Similarly, many modifications to the CG equation have been proposed, such as use of lean body mass when estimating GFR in obese patients, but this too has not been validated.[27]

Table 2 | Assessment of kidney function

Recommendations	
Clinical practice	1. Glomerular filtration rate (GFR) should be the standard measure to evaluate kidney function for staging of CKD and drug dosing purposes 2. Clinicians should use the most accurate method/tool to assess kidney function for the individual patient (i.e., eCL_{cr} or eGFR or mGFR) 3. Timed clearances of creatinine and urea may be particularly of value for patients with AKI 4. Metrics to determine the most accurate eGFR methodology include rigor of development process, comparison to gold standard, and measures of bias, precision, and accuracy in multiple patient populations 5. Clinical laboratories should report eGFR in ml/min as well as ml/min per 1.73 m^2
Research	1. Studies are needed to determine the best method to individualize drug dosing to body size 2. In AKI, studies are needed to establish the role of new biomarkers in detecting early changes in GFR
Regulatory	1. GFR should be measured directly with an inert tracer (e.g., inulin, iohexol, iothalamate, etc.) to determine the relationship between pharmacokinetic or pharmacodynamic alterations due to kidney dysfunction and GFR 2. If GFR is measured directly during pharmacokinetic and pharmacodynamic studies, then whatever method of eGFR that is used clinically for drug dosing will always be referenced to a measured GFR 3. Drug labels should refer to measured or estimated GFR without specifying the methodology to be used for drug dosing

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eCL_{cr}, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate.

The Modification of Diet in Renal Disease (MDRD) Study equation was developed from an extensive sample of patients with CKD, all of whom had a measured GFR using urinary clearance of ^{125}I iothalamate of <90 ml/min per 1.73 m^2 (ref. 28). This equation is now widely reported by clinical laboratories around the world whenever S_{cr} is reported.[29] The MDRD Study equation has been shown to overestimate measured GFR in those with values >60 ml/min per 1.73 m^2, and hence specific values are only reported for values <60 ml/min per 1.73 m^2 (ref. 29). The CKD-Epidemiology Collaboration (CKD-EPI) equation was recently developed specifically to overcome this limitation. It is more accurate than the MDRD Study equation, particularly at higher levels of GFR.[17,30] The CKD-EPI equation is now reported by Quest and LabCorp, the two largest laboratory service providers in the United States, and with it the GFR estimates are now reported throughout the GFR range.

Hence, which one of the many GFR estimation equations should be used for assessment of an individual patient's GFR as the guide to the degree of adjustment of their drug dosage regimens? The pros and cons of the various GFR-estimating equations have been extensively reviewed and there is no compelling evidence of the superiority of any given method for drug dosing in all patient populations or clinical situations.[27,31–35] Most of these studies have all compared the equations with each other in hypothetical simulations and not with actual drug clearance.[36–44] The National Kidney Disease Education Program (NDKEP) in the United States recommends that the GFR estimated from the MDRD Study or CL_{cr} estimates from the CG equation for adults or the Schwartz equation for children can be used for drug dosing.[22] For very large or very small people, they recommend adjustment of the estimated GFR (eGFR) from the MDRD Study equation to account for patient's body surface area (BSA) ($(eGFR_{IND} = eGFR_{MDRD} \times (BSA \text{ per } 1.73\ m^2))$ to yield a $eGFR_{IND}$ in units of ml/min.[25,34]

It is most important that clinicians have ready access to at least one GFR estimate for all of their patients. Currently, the CKD-EPI method is the most accurate method for estimation of GFR,[17] and it appears to be emerging as the method of choice for the staging of CKD. Although documentation of its utility for drug dosing is limited,[45] it is likely to be similar to the MDRD Study equation given the similar performance at lower levels of GFR, where dose adjustment is frequent. Clinicians should use the method that provides the most accurate assessment of GFR. In particular, this is of utmost importance for those drugs with a narrow therapeutic index for which dosing individualization is required. In those clinical situations where any creatinine-based estimation equation is not likely to provide a good estimate of GFR, measured creatinine clearance or measured GFR using exogenous markers should be considered (Table 2).[22]

DRUG DOSING CONSIDERATIONS FOR PATIENTS WITH CKD

Despite numerous published guidelines[46–51] regarding drug dosing for patients with reduced kidney function, there is insufficient evidence to guide decisions on many commonly used drugs. Indeed, occasionally recommendations derived from postmarketing studies are in conflict with the information in the official FDA or EMA product labeling and in recommendations found in frequently utilized reference sources. Before 1998, there were no official guidances regarding the explicit criteria for characterization of the relationship between drug PK and PD and kidney function. The FDA industry guidance issued in May 1998,[52] and the EMA guidance of 2004,[53] provided frameworks to help companies decide when they should conduct such a study and proposed explicit recommendations for study design, data analysis, and interpretation of the study results in product labeling.

PK and PD data

The primary literature is replete with studies of the effect of CKD on the PK or PD of many of the most commonly prescribed medications. There are however many challenges associated with the application of these data in clinical practice. The volume of distribution (V_D) of many drugs is

increased in patients with moderate to severe CKD as well as in those with preexisting CKD who develop AKI.[2,54,55] This increase in V_D may be the result of decreased protein binding, increased tissue binding, or alterations in body composition (for example, fluid overload). There is now good preclinical and emerging clinical evidence that CKD may lead to alterations in nonrenal clearance of many medications as the result of alterations in the activities of uptake and efflux transporters as well as cytochrome *P*450 (CYP enzymes) in the liver and other organs.[56–58] Prediction of the effect of impaired kidney function on the metabolism of a particular drug is however difficult and there is currently no quantitative strategy to predict changes for one drug based on data from another in the same class.

Patients with CKD may experience accumulation of metabolite(s) as well as the parent compound. This may result in unforeseen consequences as the metabolites of some drugs have significant pharmacologic activity. However, the PK and PD of metabolites are not often fully elucidated during clinical trials. Thus, the patient with CKD is being exposed to a new pharmacologic entity as the sum of the serum concentrations of the metabolite(s) and the parent compound are markedly different than those reported in patients with normal renal function.

The metabolite may have pharmacologic activity similar to that of the parent drug and thus contribute significantly to clinical response. Alternatively, the metabolite may have qualitatively dissimilar pharmacologic action; for example, normeperidine has central nervous system stimulatory activity that has caused seizures in some with CKD and AKI.[59] Because of the multiplicity of potential interactions of compounds that are primarily metabolized, the practical consequences of metabolite accumulation are difficult to predict.

Goals of therapy

The desired dosage regimen adjustment goals for some agents are drug class specific. The desired goal may be: the maintenance of a similar peak, trough, or average steady-state drug concentration or for antibiotics an optimized PD measure such as the time above the minimum inhibitory concentration or the ratio of the drug area under the concentration time curve (AUC) to the minimum inhibitory concentration.[60] When there is a significant relationship between drug concentration and clinical response[61] (for example, aminoglycosides) or toxicity[62] (for example, phenytoin), then attainment of the specific target values becomes critical. If, however, no specific PK or PD target values have been reported, then a regimen goal of attaining similar average steady-state concentrations may be appropriate.

Drug dosage regimen individualization

Most dosage adjustment guidelines have proposed the use of a fixed dose or interval for patients with broad ranges of kidney function that are different from those that are the foundation of the current CKD classification system.[54,55,63–65] Indeed, in the FDA guidance, normal kidney function has often been ascribed to anyone who has a $CL_{cr} > 80$–90 ml/min. In addition, mild, moderate, and severe impairments in kidney function are often defined differently among the PK studies, and each of these categories often encompasses a broad range of kidney function. The drug dosage adjustment recommendations that use broad ranges of kidney function may not be optimal for all patients whose kidney function lies within the range especially for agents that have a narrow therapeutic index.

Developing drug dosage adjustment recommendations for the CKD patient is often predicated on the attainment of the desired exposure goal (see above) at steady state that will surely be delayed because of the reduced clearance and prolonged half-life of the drug. In order to achieve the desired goal in a timely fashion, a stepwise approach that includes multiple considerations (see Table 3) for each individual drug has been proposed.[49] Indeed, in some patients, the clinical circumstance may suggest that a lower or higher dose be used than is indicated by the drug dosing guidelines. The following parameters may help guide individual therapy.

Loading dose. Most published guidelines do not recommend a loading dose, despite the well-documented evidence of altered V_D of several drugs in CKD patients. Loading doses may be required if a drug has a long half-life and there is a need to rapidly achieve the desired steady-state concentrations. Furthermore, if the V_D of a drug is significantly increased in CKD patients, a loading dose will likely be needed even if one was not routinely recommended for those with normal renal function. If the relationship between V_D and CL_{cr} has been characterized, then the V_D should be estimated from that relationship. If that is not the case, a modified loading dose can be calculated if one knows the degree of change in the V_D.

$$\text{Patient's loading dose} = \text{Usual loading dose} \times [(\text{Patient's } V_D)/(\text{Normal } V_D)] \quad (1)$$

Maintenance dose. The predicted V_D may be used with the predicted elimination rate constant (k) or total body clearance (CL_T) of the drug to yield an adjusted dosing interval and maintenance dose when one desires to achieve a specific target serum concentration.[5,6,58] If the goal of a maintenance dosing regimen is however to attain a similar steady-state drug concentration time profile, that is, AUC, as would occur if the patient had normal kidney function, a simple proportional approach can be utilized. In general, prolonging the dosing interval but maintaining the same dose will result in the achievement of similar peak and trough concentrations as well as AUC and thus may be preferred.

Measurement of therapeutic drug levels. Measuring drug concentrations is one way to optimize therapeutic regimens and account for changes between and within individuals.

Table 3 | Stepwise approach to adjust drug dosage regimens for patients with CKD and AKI

Step 1	Obtain history and relevant demographic/clinical information	Assess demographic information, past medical history including history of renal disease, and current clinical and laboratory information, including DNA polymorphisms to ascertain drug therapy needs
Step 2	Estimate GFR	Use most appropriate tool to assess eGFR or CL_{cr} for the patient based on age, body size, ethnicity, and concomitant disease states
Step 3	Review current medications	Identify drugs for which individualization of the treatment regimen will be necessary
Step 4	Calculate individualized treatment regimen	Determine treatment goals (see text); calculate dosage regimen based on pharmacokinetic characteristics of the drug and the patient's volume status and eGFR or CL_{cr}
Step 5	Monitor	Monitor parameters of drug response and toxicity; monitor drug levels if available/applicable
Step 6	Revise regimen	Adjust regimen based on drug response or change in patient status (including renal function) as warranted

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; CL_{cr}, creatinine clearance; eGFR, estimated GFR; GFR, glomerular filtration rate.

Therapeutic drug monitoring requires availability of rapid, specific, and reliable assays and known correlations of drug concentration to therapeutic and adverse outcomes. In addition, hypoalbuminemia may influence interpretation of drug concentrations as the total drug concentration may be reduced even when the active unbound drug concentration is not. Unbound drug concentrations are often not clinically available, and therefore clinicians must empirically consider the impact of hypoalbuminemia in their interpretation of measured total drug concentrations (Table 4).[55,66,67]

DRUG DOSAGE CONSIDERATIONS FOR PATIENTS WITH AKI

Critically ill patients frequently develop AKI, multiorgan dysfunction syndrome (MODS), or multisystem organ failure (MSOF).[3,68–70] Although most cases of MSOF/MODS occur secondary to shock, sepsis, and severe trauma, a multiplicity of other risk factors have been identified. Over 90% of patients who develop MSOF/MODS have early respiratory dysfunction. Cardiac dysfunction is often observed shortly thereafter, followed by hepatic dysfunction within 4–6 days and AKI in 5–7 days. Unfortunately, there are large gaps in knowledge of drug metabolism and disposition in patients with MSOF/MODS as well as AKI, and thus patients may be at significant risk for underdosing as well as overdosing.

PK and PD data

The application of PK principles involving changes in absorption, distribution, metabolism, and excretion is the first step to optimizing drug therapies for patients with AKI, MSOF, or MODS.[71,72] Critically ill patients typically have minimal oral intake of food and liquids and rely upon intravenous fluids for fluid maintenance and nutrition. In addition, H2-antagonists and proton pump inhibitors are used for stress ulcer prophylaxis and they significantly increase the gut pH. Any orally administered drug needing an acidic environment for dissolution may thus not be readily absorbed. Other absorption-altering conditions such as slow gastrointestinal motility, prolonged intestinal transit times, bacterial colonization, and necrotizing enterocolitis (seen in neonates) have also been noted in these patients. Thus, intravenous administration of drugs may need to be considered to assure appropriate absorption.

Drug distribution is one of the most important, yet the most complicated, physiologic variable to quantify for patients with AKI, MSOF, or MODS. There is a fine balance between detrimental fluid overload and adequate hydration to preserve kidney perfusion. Numerous studies in both adult and pediatric patients have concluded that critically ill patients should early on be managed in a slightly negative fluid balance after initial adequate fluid resuscitation.[68,73–75] However, in patients prone to low blood pressure, this may not be prudent. Careful and frequent reassessment of volume status is mandatory in this patient situation.

Multiple animal[57,76–78] and a few human studies[57,79–82] have demonstrated a reduction in the transcription and/or metabolic activity of hepatic and intestinal CYP450 in CKD patients. The impact of AKI, MSOF, and MODS on drug metabolism is delayed in onset or minimal in the majority of studies,[83–85] whereas nine studies did not demonstrate any impact on hepatic metabolic activity.[86–94] The remaining four studies revealed either an increase or a decrease in hepatic metabolic activity.[95–98] Definitive conclusions on the PK of metabolized medications in AKI remain hampered by the clinical complexity and potential confounders in the critically ill patients. Hypoxia, decreased protein synthesis, competitive inhibition from concomitant medications, and decreased hepatic perfusion could also be explanations for the reduced clearance.

Patient assessment

Hyperfiltration and massive overhydration are often evident early in the course of MSOF/MODS, especially in those with burns or trauma, and can lead to the use of inappropriately low doses of medication, treatment failure, and even death.[99] Hypofiltration and GFR may be especially challenging to quantify in those with rapidly changing function.[8,51] Finally, estimation or measurement of GFR may not provide an accurate measure of the contribution of the kidney to the excretion of all drugs, especially those that are extensively secreted and/or metabolized in the kidney or other organs.[100,101] Several new quantitative techniques and assessment protocols have been developed and utilized in patients with 'stable' CKD, liver disease, and some other conditions.[102–104] The potential benefits of these methods

Table 4 | Drug dosing considerations for patients with CKD

Recommendations	
Clinical practice	1. A single tool to evaluate kidney function for determination of CKD and drug dosing purposes would enable delivery of high-quality care 2. It should be recognized that drug dosing recommendations developed in the era of high serum creatinine variability will be applied differently than intended in the original pharmacokinetic study 3. Clinicians should use the most appropriate tool to assess kidney function for individual patient (i.e., measured vs. estimated) 4. Metrics to determine most accurate eGFR include rigor of development process, comparison to gold standard, and measures of bias, precision, and accuracy 5. Clinical laboratories should also report eGFR in ml/min 6. Drug dosages should be adjusted according to FDA- or EMA-approved product labeling 7. When there is no information in the product label, peer-reviewed literature recommendations should be used to guide drug dosage regimen adjustments 8. Obese CKD and AKI patients and those with large variations in serum protein levels should have their drug dosage individualized based on the best available evidence
Research	1. Rigorously conducted PK/PD studies are needed to evaluate the impact of CKD on all drugs. The analysis of these studies should generate dosage regimen recommendations based on continuous relationship between GFR and clearance as well as V_D when evident 2. Categorical dosage recommendations should be based on pharmacokinetic and exposure response, not predetermined categories of kidney function 3. Evaluate the relationship between steady-state drug and metabolite exposure when appropriate on drug safety and efficacy in patients with CKD enrolled in phase II and III and/or postmarketing studies 4. Evaluate the impact of interactions of all drugs commonly used in CKD patients (e.g., phosphate binders, PPI) 5. Design and test methods to translate knowledge of PK/PD and drug interactions into clinical practice (e.g., clinical decision support systems) 6. Develop database of patients with CKD with PK/PD data and outcomes (safety/efficacy) data 7. Examine differences in dosing efficacy and safety related to the use of various kidney function indices
Regulatory	1. Drug labeling should state the strength of evidence for dosing modifications for CKD patients 2. Pharmacokinetic studies in healthy normal volunteers and CKD stage 1–5 patients should be conducted for all renally eliminated drugs 3. Reduced PK studies should be performed for all drugs. Study population should include patients on HD and the study should be initiated on a non-HD day 4. Measured GFR should be the standard for renal function and the relationship between PK/PD parameters and multiple estimating equations should be assessed 5. Pharmacokinetic data from CKD patients provided to FDA should be publicly available and accessible in user-friendly format 6. Drug labels should indicate the dosage recommendations based on measured GFR rather than a specific estimation equation 7. Further evaluations of the safety and efficacy of the proposed dosage regimens should be assessed in postmarketing studies in patient populations not sufficiently represented in premarketing studies

Abbreviations: AKI, acute kidney injury; CKD, chronic kidney disease; eGFR, estimated GFR; EMA, European Medicines Agency; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; HD, hemodialysis; PD, pharmacodynamics; PK, pharmacokinetics; PPI, proton pump inhibitors; V_D, volume of distribution.

include an improvement in dosage individualization and identification of the mechanisms responsible for nephrotoxic injury. Although both methods have been validated, there has been no subsequent published data regarding their application in patients with CKD, AKI, or MSOF/MODS.

Assessment of kidney function in patients with AKI or MSOF/MODS is challenging.[105–107] Any endogenous filtration marker, such as creatinine, needs to be measured at steady state before it can provide a reliable estimate of GFR. Hence, no estimating equations can provide an accurate estimate of GFR in AKI. The rate of change of S_{Cr} or eGFR may provide some insight but this cannot be used as a quantifiable measure, and such values cannot be applied to individual patient situations as multiple events are typically happening concurrently. Another strategy to estimate GFR in AKI is to measure creatinine clearance with incorporation of the mean of the beginning and ending S_{cr} value as an estimate of GFR. Shorter time periods than 24 h may be appropriate in patients with rapidly changing levels of kidney function. For patients with MSOF/MODS without AKI, S_{cr} and all related estimating equations are likely to overestimate the GFR or creatinine clearance because of the influence of non-GFR determinants in these clinical scenarios.

There is a paucity of dosing algorithms to guide pharmacotherapy, derived from investigations of the PK/PD of medications, in patients with AKI or MSOF/MODS.[64,72,108] Indeed, most of the critical care literature and almost all FDA or EMEA product labeling contains drug dosage recommendations that were derived from observations in patients with CKD or those receiving RRT. The limited data from these populations that are available have predominantly been developed by clinicians who have gained experience with a given drug after it has been approved for marketing, and rarely, if ever, is this information incorporated into official product labeling. Thus, it is challenging for clinicians to individualize therapy when the available PK/PD information is so scant. It is near impossible to provide the best dosage regimen for AKI or MSOF/MODS patients

because of their fluctuating kidney function, volume status, and potentially metabolic activity.

Drug dosing approaches

The principles of drug dosage regimen modification previously described for use in CKD patients are the foundation for those with AKI or MSOF/MODS.

Loading dose. As the V_D of many drugs, especially hydrophilic antibiotics, including β-lactams, cephalosporins, and penems, are significantly increased in the presence of AKI, the administration of aggressive loading doses (25–50% greater than normal) are highly recommended.

Maintenance dose. Clinical judgment is paramount and forecasting the degree and rate of change in kidney function and fluid volume status is fraught with uncertainty. Because of the preservation of nonrenal clearance for some agents such as vancomycin, imipenem, and ceftizoxime, as well as the tendency to attain a positive fluid balance in the early stages of AKI, the dosing regimen for many drugs, especially antimicrobial agents, should be initiated at normal or near-normal dosage regimens.

Therapeutic drug monitoring. Prospective measurement of serum drug concentrations and the subsequent use of sound PK/PD therapeutic drug monitoring approaches should be used whenever possible, especially for drugs with a narrow therapeutic range. When this is not a possibility because of the unavailability of rapid specific analytical methods for the determination of serum drug concentrations, the development of excessive pharmacologic effect or toxicity may be the primary indicator of a need for dosage adjustment. Finally, there are currently very limited data to guide drug dosing for AKI or MSOF/MODS patients receiving one of the multiple variants of RRT (Table 5).[64,72,108]

DRUG DOSING CONSIDERATIONS FOR HD PATIENTS

The optimization of pharmacotherapy for patients receiving intermittent HD is critically dependent on the availability of reliable information from well-designed PK studies. The artificial kidney is an ideal eliminating 'organ' because, in contrast to renal or hepatic routes of drug elimination, blood flow to the dialyzer, drug concentrations in blood entering and leaving the dialyzer, and recovery of eliminated drug can all be measured.[109]

PK and PD data

Although many hemodialyzers have been introduced in the past 10 years, and more than 100 different ones were available in the United States in 2011, the effect of HD on the disposition of a drug is rarely evaluated more than once. Thus, most of the literature, especially for older medications, probably represents an underestimation of the impact of HD on its disposition.[110]

The impact of HD on a patient's drug therapy is dependent on several factors, including the drug characteristics, the dialysis prescription, and the clinical situation for which dialysis is performed. Drug-related factors include the molecular weight or size, degree of protein binding, and distribution volume.[2,62] The vast majority of dialysis filters in use until the mid 1990s were composed of cellulose, cellulose acetate, or regenerated cellulose (cuprophane); and they were generally impermeable to drugs with molecular weights >1000 Daltons.[109] The HD procedure prescription can dramatically affect the dialysis clearance of a medication.[111] The primary factors that vary between patients are the composition of the dialysis filter, the filter surface area, the blood, dialysate and ultrafiltration rates, and whether or not the dialysis unit reuses the dialysis filter. Dialysis membranes in the twenty-first century are predominantly composed of semisynthetic or synthetic materials (for example, polysulfone, polymethylmethacrylate, or polyacrylonitrile). High-flux dialysis membranes have the larger pore sizes and this allows the passage of most solutes, including drugs that have a molecular weight of $\leqslant$20,000 Daltons.[109,110]

The impact of HD is not strictly limited to dialysis clearance. There is evidence that some drugs adhere to the dialyzer membrane, and recent findings suggest that the nonrenal clearance (metabolism) of some agents is altered by HD. A single 4-h session of HD increased the nonrenal clearance of erythromycin in patients with end-stage renal disease by 27% as soon as 2 h after HD.[112] This was presumably secondary to the removal of uremic solutes that accumulate during the interdialytic period and inhibited *CYP450* 3A4 and drug transporters. A subsequent study of midazolam in subjects with end-stage renal disease implicated transporters (human organic anion-transporting polypeptide and/or intestinal P-glycoprotein) as the likely drug disposition bottleneck in uremia rather than CYP3A4.[56] Should CL_{NR} actually increase during HD, this would lead to an overestimation of CL_D.

Assessment of the impact of HD

The most common method for assessing the effect of HD is to calculate the dialyzer clearance (CL_D) of the drug; CL_D^b from blood can be calculated as $CL_D^b = Q_b[(A_b - V_b)/A_b]$, where Q_b is blood flow through the dialyzer, A_b is the concentration of drug in blood going into the dialyzer, and V_b is the blood concentration of drug leaving the dialyzer.[113–117] This equation, which has been termed the 'A-V difference method,' is only valid if the drug concentrations are measured in whole blood and if the drug rapidly and completely distributes into red blood cells. Because drug concentrations are generally determined in plasma, the previous equation is usually modified to $CL_D^p = Q_p[(A_p - V_p)/A_p]$ where p represents plasma and Q_p is plasma flow, which equals Q_b (1−hematocrit). This equation tends to underestimate HD clearance for drugs that readily partition into and out of erythrocytes. In addition, venous plasma concentrations may be artificially high if extensive ultrafiltration is performed and thus CL_D^p will be low if plasma water is removed from the blood at a faster rate than drug.

Table 5 | Drug dosing considerations for patients with AKI

Recommendations	
Clinical practice	1. The KDIGO AKI, AKIN, RIFLE, or pRIFLE criteria should be prospectively utilized to optimize the identification of patients at highest risk of developing AKI 2. High-risk medications, those with known nephrotoxicity, or other potential toxicities associated with supratherapeutic serum concentrations should be identified proactively, for example, computerized order entry, so that the prescribing clinician can closely monitor patient response 3. The volume of distribution of several medications is dramatically increased in the presence of AKI and thus larger loading doses may need to be administered to avoid subtherapeutic responses due to the achievement of lower than desired serum concentrations 4. When possible, therapeutic drug monitoring should be utilized for those medications where serum drug concentrations can be obtained in a clinically relevant time frame 5. Trends in renal function indices such as serum creatinine and urine output along with volume status should be utilized to guide drug dosing when rapidly measurable indices are unavailable 6. For those medications where therapeutic drug monitoring is not possible, close monitoring of drug PD may prove to be a useful surrogate 7. Evaluation of risk for drug–drug and drug–nutrient interactions should be facilitated by incorporating validated electronic drug interaction tools into EMRs 8. A patient-centered team approach that includes an ICU pharmacist is recommended to prevent medication-related problems and enhance safe and effective medication use 9. EMRs should maintain records for discontinued medications for up to 7 days to make it possible to assess potential residual effects on the patient's current condition
Research	1. Evaluate the sensitivity and reliability of biomarkers to predict risk for the development of AKI and quantify the degree of injury 2. Formulation and validation of rapid and reliable direct measurement methods or estimating formulas for kidney and liver function are definitively needed to prospectively ascertain the trajectory of the patient's kidney or liver function 3. Generate guidelines for the frequency of prospective monitoring of kidney function and drug dosing adjustments in patients with AKI 4. If estimating equations are to be used, these should be validated against measured values determined via state-of-the-art standard techniques for assessing kidney function 5. Clinical studies of nonrenal clearance of the most commonly used metabolized medications and the most important hepatic enzymes, CYP2D6, 2C9, 2C19, and 3A4 in AKI are imperative given the emerging evidence that the activity of these enzymes are altered in the presence of CKD 6. Specific and rapid drug assays (LC-MS/MS) for high-risk medications should be developed and widely available so that pharmacokinetic studies of medications used in AKI patients receiving and not receiving various RRTs can be conducted 7. Development and validation of 'standardized ICU drug assay panels' (e.g., multiple antibiotics) to facilitate therapeutic drug monitoring to optimize patient outcomes. Validation should include assessment of assay interference with commonly used medications in AKI patients 8. Encourage further development of electronic tools/decision-making software to guide drug dosage individualization and detect, ascertain causality, and prevent drug interactions 9. Create open-access databases, based on FDA Medwatch system, to collect information regarding potential drug adverse events and drug interactions in AKI patients 10. Develop a longitudinal medication history to aid in the identification of residual effects of drugs on the pharmacokinetics, dynamics as well as the patient's sensitivity to the development of adverse events 11. Create a mechanism to enroll AKI patients upon ICU admission into PK and PD studies across the spectrum of AKI
Regulatory	1. PK and PD studies of all medications in patients with stage 3–5 AKI should be conducted so that reliable drug dosing recommendations can be developed 2. The innovator of a new drug likely to be used in the ICU setting should during the drug development process establish methodologies for the analysis of drug concentrations in the clinical setting so that the value of TDM in AKI patients can be assessed 3. Drug labeling should state the level of evidence for the safe and effective use in AKI 4. Mandate changes in drug labeling to reflect measurement techniques used for establishing the patient's organ clearance that are the foundation of drug dosing individualization 5. Mandate postmarketing studies to validate drug clearance relationships with 'standard' organ function assessments performed in stable patients with chronic disease are relevant in the setting of MODS

Abbreviations: AKI, acute kidney injury; AKIN, Acute Kidney Injury Network; CKD, chronic kidney disease; EMRs, electronic medical records; FDA, US Food and Drug Administration; ICU, intensive care unit; KDIGO, Kidney Disease: Improving Global Outcomes; LC-MS/MS, liquid chromatography/mass spectrometry; MODS, multiorgan dysfunction syndrome; PD, pharmacodynamics; PK, pharmacokinetics; RRT, renal replacement therapy; RIFLE, risk, injury, failure, loss, end-stage kidney disease; pRIFLE, pediatric risk, injury, failure, loss, end-stage kidney disease; TDM, therapeutic drug monitoring.

Because of the above limitations, the recovery clearance approach remains the benchmark for the determination of dialyzer clearance and it can be calculated as:[2,115,116] $CL_D^r = R/AUC_{0-t}$ where R is the total amount of drug recovered unchanged in the dialysate and AUC_{0-t} is the area under the predialyzer plasma concentration–time curve during the period of time that the dialysate was collected. To determine the AUC_{0-t}, a minimum of three to four plasma concentrations should be obtained during dialysis.

The HD clearance values reported in the literature may vary significantly depending on which of these methods were used to calculate CL_D. The principal reason for this is that for most medications we do not know the degree and rapidity with which the drug crosses the red blood cell membrane.[2,110,113] Because the CL_D^r method incorporates no

Table 6 | Drug dosing considerations—hemodialysis

Recommendations	
Clinical practice	1. The dose should be given after dialysis (D_{hd}) to ensure active drug levels until next dosing. Consider a supplementary (D_{sup}) dose in addition to the dose adjusted to kidney failure (D_{fail}) after dialysis to replace the fraction removed by dialysis (F_r) $D_{hd}=D_{fail}+D_{sup}$ where $D_{sup}=F_r$ ($D_{start}-D_{fail}$) 2. The D_{sup} derived from studies of low-flux nonsynthetic membranes should empirically be increased by at least 50% when patients are dialyzed with high-flux synthetic dialyzers 3. Extended dialysis regimens with high diffusive membranes have been associated with extensive drug clearances and thus the D_{sup} may need to be increased
Research	1. Develop accurate and reproducible methods to quantitate dialysate and ultrafiltration flow rates and collect representative aliquots because the clinical utility of pharmacokinetic studies in HD patients is critically dependent on the accuracy of these procedural variables 2. Develop methodologies to quantitate the degree of drug adsorption to the dialyzer membrane and associated elements in the extracorporeal circuit as this route of drug removal impacts the overall dialyzer clearance 3. The drug should be administered intravenously at a sufficient interval before HD is instituted so that predialysis distribution and elimination PK can be fully characterized 4. The dialyzer model and all the components of the dialysis prescription should be reported for each individual studied. The dialysis prescription should be standardized as much as clinically feasible to enhance the generalizability of the data 5. The time course and the extent of the postdialysis rebound in drug serum concentrations should be assessed and the resultant data incorporated into the drug dosage regimen recommendation
Regulatory	1. FDA and EMA should mandate that the PK/PD including determination of the HD clearance be evaluated for all drugs that will likely be used in ESRD patients 2. *In vitro* and *in vivo* dialysis studies should use a standard array of model substrates such as creatinine, vitamin B12 or vancomycin, and β2-microglobulin. This will facilitate extrapolation of the results with one hemodialyzer to another as it is impractical to mandate studies be done with all commercially available dialyzers

Abbreviations: EMA, European Medicines Agency; ESRD, end-stage renal disease; FDA, US Food and Drug Administration; HD, hemodialysis; PD, pharmacodynamics; PK, pharmacokinetics.

assumption of the degree of red blood cell permeability, it can be reliably used as the benchmark value. The primary limitation of this calculation is that the concentrations of the drug in the dialysate may be below the sensitivity limits of the assay. A continuing clinical problem is that PK results obtained with one dialyzer are generally not representative of the performance of another dialyzer.[2,110] 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 a different dialyzer.[118] Therapeutic drug monitoring, including measurement of the dialyzer clearance, should be utilized for drugs with a narrow therapeutic range, for example, aminoglycosides and vancomycin. Finally, drug dosage recommendations derived from studies conducted before 2000 likely represent an underestimate of the impact of HD and dosages may need to be empirically increased by 25–50% (Table 6).

DRUG DOSING CONSIDERATIONS FOR PATIENTS RECEIVING CRRT

Continuous renal replacement therapy (CRRT) is commonly used to manage hemodynamically unstable AKI patients. Several modes of therapy (convective, diffusive, or both), a variety of filter materials, and different effluent flow rates are used,[111,119] all of which can influence drug removal.

PK and PD data

Despite the large variability in CRRT techniques, a review of published clearance studies found that <90% of studies specified the prescribed CRRT dose and only 58% of continuous venovenous hemofiltration studies specified whether pre- or post-dilution mode was used.[120] Two basic PK values necessary for interpretation of study results, V_D and 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.

Hybrid RRTs that utilize higher dialysate flow rates than those used in CRRT, and shorter treatment periods (6–12 h in duration), are frequently prescribed as well. Hybrid therapies include slow low-efficiency dialysis (SLED), extended daily dialysis, continuous SLED, slow low-efficiency daily dialysis (SLEDD), and slow low-efficiency daily hemodiafiltration (SLEDD-f). Finding relevant literature for application to a given clinical situation is thus challenging and PK interpretation difficult.[121–125] The intermittent nature of most hybrid RRTs can further complicate drug dosing, as higher doses may be needed during the therapy, whereas lower doses may be adequate during therapy downtime. To date, hybrid RRT PK data have been published for only 12 drugs.[126–139]

Assessment of the impact of CRRT and hybrid RRT

CRRT parameters substantially influence drug clearance. The mode of therapy (diffusion, convection, or both) can be influential, as both therapy modes can remove small solutes, but convective therapies are superior at removing larger solutes.[140,141] Drug clearance is affected by where replacement fluids are given, because this influences the drug concentration within the filter. Mathematical calculations can account for this,[142–144] but published studies do not always specify this information.[120] Filter composition can also influence drug removal.[145,146] Some degree of drug

Table 7 | Drug dosing considerations for AKI patients receiving CRRT/EDD

Recommendations	
Clinical practice	1. ESRD dosing recommendations should be used only as an initial guide for the initiation of therapy in an AKI patient receiving CRRT when no other information is available 2. The existing maintenance dosing recommendations for ESRD patients receiving HD often result in the achievement of subtherapeutic concentrations and treatment failures for patients with severe AKI requiring RRT 3. The most effective dosing optimization strategy is to use therapeutic drug monitoring for drugs like aminoglycosides and vancomycin to achieve the desired therapeutic goals. However, very few drugs have clinically useful (quick turnaround time, FDA/EMA approved) assays available 4. When CRRT or EDD clearance data are available, the current literature recommendations should be the logical starting dose for therapy. Different treatment intensities for CRRT or EDD result in marked variability in drug removal and thus this literature may not be generalizable across the multiple CRRT and EDD prescriptions that are used in practice 5. Another alternative is to calculate the 'total creatinine clearance' (CL_{cr}) based on the addition of the patient's residual renal clearance and expected extracorporeal clearance. This value can then be used to estimate a maintenance dosing regimen based on medication dosing guidelines specified for that resultant total CL_{cr} range. Using this method, most drugs will fall in the CL_{cr} 25–50 ml/min range 6. 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 (Fr_{EC}) i. Maintenance dose=anuric dose/$[1-Fr_{EC}]$ ii. Dosing interval=anuric dosing interval $\times [1-Fr_{EC}]$ 7. A fifth method starts with a normal dose (D_n) and reduces dose based on normal clearance (Cl_{norm}), non-renal clearance ($Cl_{nonrenal}$), effluent rate (Q_{eff}), and sieving coefficient (SC) b. Dose $=Dose_n \times [Cl_{nonrenal}+(Q_{eff} \times SC)]/Cl_{norm}$ 8. CRRT and EDD education should be an integral part of critical care and nephrology fellowship training programs
Research	1. CRRT or EDD clearance data derived from *in vitro* studies or those conducted in ESRD patients are needed to guide clinical studies in AKI patients 2. Studies should be conducted in AKI patients to characterize the influence of CRRTs because the PK parameters observed in ESRD patients are not generalizable to ICU patients
Regulatory	1. FDA and EMA should mandate PK/PD studies at a given, predefined CRRT or EDD intensity level during the preapproval process or in phase IV studies 2. FDA and EMA should make PK/PD studies a mandatory requirement for antimicrobials and renally excreted drugs that are likely to be extensively used in the ICU setting 3. Available and future PK/PD data in this patient population should be compiled in a publicly accessible data repository 4. The effect of other extracorporeal techniques should be investigated in terms of their ability to remove/adsorb drugs 5. The results of PK/PD studies conducted in patients receiving CRRT/EDD and dosing guidelines for these therapies should be presented in a drug's package insert

Abbreviations: AKI, acute kidney injury; CRRT, continuous renal replacement therapy; CVVH, continuous venovenous hemofiltration; EDD, extended daily dialysis; EMA, European Medicines Agency; ESRD, end-stage renal disease; FDA, US Food and Drug Administration; GFR, glomerular filtration rate; HD, hemodialysis; ICU, intensive care unit; PD, pharmacodynamics; PK, pharmacokinetics; RRT, renal replacement therapy.

adsorption occurs with many CRRT membranes (particularly sulfonated polyacrylonitrile and polymethylmethacrylate), although it is difficult to quantify adsorption in both *in vitro* and *in vivo* studies.[95,147,148] Dialysis dose is one of the most influential factors, with increased dialysate/ultrafiltration/effluent flow rates resulting in greater drug removal.[146,147]

Drug dosing approaches

The clinical desire to deliver higher RRT doses as well as the improvement of RRT machines and filters has rendered old dosing guidelines for drugs, especially antibiotics, ineffectual and potentially dangerous.[55,64] PK studies conducted in critically ill patients receiving CRRT or hybrid RRT are rare and dosing guidelines for these therapies are not often presented in a drug's product labeling. There are several published dosing recommendation guidances that are widely used.[62,64,108,149,150] These recommendations have not been prospectively tested to see if their application increases the attainment of therapeutic target serum concentrations or, more importantly, patient outcomes. The limitations of those calculations are illustrated by the fact that two different recommended doses for some antibiotics differ by up to an order of magnitude (Table 7).

DRUG DOSING CONSIDERATIONS FOR PATIENTS RECEIVING PERITONEAL DIALYSIS

Peritoneal dialysis as practiced in 2011 is very unlikely to enhance total body clearance of any drug by more than 10 ml/min, as most typical peritoneal dialysis prescriptions are designed to achieve a urea clearance of $\sim$10 ml/min. As most drugs are larger than urea, their clearance is even less; thus, drug clearance will likely be in the range of 5 to 7.5 ml/min. Many studies performed in the 1970s and 1980s showed that drug clearances by peritoneal dialysis were in this range, and thus one can conclude that peritoneal dialysis does not enhance drug removal to a degree that will require a dosage regimen modification.[151–154] Therefore, drug therapy recommendations for those with CL_{cr} or eGFR <15 ml/min are likely clinically useful.

PK and PD data

In patients with established peritoneal dialysis, the access to the peritoneal cavity provides an opportunity to deliver drugs

Table 8 | Drug dosing considerations—peritoneal dialysis

Recommendations	
Clinical practice	1. As most pharmacokinetic studies establishing peritoneal antibiotic doses have used 4- to 8-h loading periods, it is recommended to perform antibiotic loading by an extended cycle in both CAPD and APD patients. For intermittent maintenance dosing, a long nighttime dwell should be used in CAPD and a long daytime dwell in APD patients 2. Intermittent antibiotic dosing has not been unequivocally successful in eradicating bacterial growth, partially questioning the concept of antibiotic back diffusion into the peritoneal cavity. Transperitoneal drug movement may be less effective in the post acute phase of peritoneal infection when inflammation-related capillary hyperperfusion subsides 3. Short dwell times in APD patients may prevent accumulation of antibiotic in the peritoneal cavity to concentrations exceeding the minimal inhibitory concentrations 4. Monitoring of drug blood levels is advocated in patients receiving intraperitoneal antibiotics because they are at increased risk for under- and over-dosing, that is, those with significant residual renal function and those on intense APD schedules, respectively. Monitoring of dialysate concentrations may provide even more relevant information
Research	1. CAPD patients are a suitable group for PK and PD studies in end-stage renal disease as they represent a steady-state clinical condition 2. Peritoneal dialysis drug clearance may need to be characterized for many more drugs than in the past due to the introduction of high- and continuous-flow peritoneal dialysis variants, which are likely to become available for both acute and chronic patients in the foreseeable future 3. Although the intraperitoneal route is a well-established administration mode for some agents, especially antibiotics in patients with peritoneal dialysis-associated peritonitis, several aspects of this dosing approach require further research. These include assessment of the degree of equivalence of drug absorption across a noninflamed vs. inflamed peritoneum and the determination of the optimal administration schedule to achieve adequate systemic drug exposure 4. Simulation studies of bidirectional transperitoneal drug transport would be particularly relevant in intermittently treated patients on automated peritoneal dialysis, in whom alternating phases of rapid nocturnal cycling and daytime rest might result in complex pharmacokinetic patterns 5. Finally, the efficacy and safety of intermittent and continuous dosing protocols should be studied in clinical trials
Regulatory	1. The limited and continuous drug clearance achieved with many modes of peritoneal dialysis does not warrant a mandate to conduct PK/PD studies of all new drugs 2. However, as the transperitoneal route is a well-established administration mode mainly for antibiotics and antifungal agents in patients with peritoneal dialysis-associated peritonitis, it is recommended that PK studies of new agents in these classes be conducted in the postmarketing period

Abbreviations: APD, automated peritoneal dialysis; CAPD, continuous ambulatory peritoneal dialysis; PD, pharmacodynamics; PK, pharmacokinetics.

both locally and systemically. The degree and rate of drug transport across the peritoneum 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 drug, the exposure time, and the peritoneal perfusion rate.[155] Intraperitoneal drug administration is well accepted for the treatment of peritoneal dialysis-associated peritonitis and other infections.[156,157] Intraperitoneal therapy appears attractive but has several potential technical pitfalls: solubility and stability of the compounds in peritoneal dialysis fluid,[158,159] and co-administration of more than one compound can lead to chemical interactions and changes in solubility. Administration intervals depend on the half-life of the drug, which is mainly determined by 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, which are suitable for once-daily dosing.[156,160,161]

Drug dosing approaches

Although the concept of intermittent antibiotic administration appears intriguing because of its practicality and cost efficiency, the efficacy and safety of intermittent dosing is impacted by several factors. Most importantly, the dialysate flow rate strongly affects the elimination of the drug.[161] In patients treated by automated peritoneal dialysis with frequent short dialysis cycles, exposure to peritoneal dialysis fluid with a given antibiotic concentration over several cycles may result in higher plasma concentrations as compared with antibiotic loading in a single extended dwell period in patients on continuous ambulatory peritoneal dialysis. Conversely, the higher dialysate flow and small molecule clearance achieved with automated peritoneal dialysis regimens may lead to a greater peritoneal clearance of antibiotic in the periods between dosing (Table 8).[157]

CONCLUSIONS AND PERSPECTIVES

The discussion of the large body of evidence by the conference participants clearly indicates that there have been significant advances in knowledge of the influence of kidney function and RRTs on drug disposition during the past 30 years. The clinical practice recommendations were made to help guide clinicians and will hopefully serve as stimuli for the establishment of further standards of practice for the enhancement of patients' clinical outcomes.

It was also clear that there were significant gaps in knowledge of the PK and PD of most drugs in AKI and CKD patients. As such, establishment of a research agenda was a focus of much of the conference. Furthermore, the evolution of RRTs mandates the inclusion of a higher level of rigor in future investigations so that the quality of the data is improved and its clinical utility enhanced. Indeed, much of

the data that are currently available are now only of historical value. The challenge is that there is no obvious source of funding for such research activities. These questions are not hypothesis driven, and thus not generally the basis for investigator-initiated grants. Industry supports much of the research that goes into the development of new drugs, but there is no mechanism at present for funding postmarketing studies in patients with kidney function impairment, especially those with AKI who are receiving CRRT. Recognition of funding sources is an important step in addressing many of these issues.

The regulatory recommendations were considered critical to the conference process as in many cases the quest to better understand the drug dosing needs of AKI and CKD patients is driven by drug-approval agency expectations of the pharmaceutical and biotechnology industry. The KDIGO Controversies Conference highlighted the gaps but more importantly focused on crafting paths to the future that will stimulate research and improve the global outcomes of patients with kidney injury and disease.

DISCLOSURE

All the authors declared no competing interests.

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