CHAPTER 3

RENAL DRUG DOSING CONCEPTS

Dean A. Van Loo and Thomas C. Dowling

Chronic kidney disease (CKD) is a progressive consequence of systemic diseases such as diabetes and hypertension as well as localized kidney injury as the result of glomerulonephritis. Over 500,000 patients in the United States have stage 5 CKD, which is also categorized as end-stage renal disease (ESRD). Each year, for the last several decades, up to 100,000 patients have developed ESRD and over 80,000 have died.[1] Chronic renal replacement therapy, whether peritoneal or hemodialysis (HD), was life-sustaining for over 600,000 patients in 2011 at a total cost of over $49 billion USD. A significant portion of patients who receive a kidney transplant continue on to develop CKD. Most stage 1 to 4 CKD patients are initially identified in primary care clinics, while others are identified in acute care environments. Population-based studies, such as NHANES, report that the prevalence of CKD is increasing dramatically, with more than 50% of U.S. adults aged 30 to 64 expected to develop CKD in their lifetime.[2]

Kidney failure can also appear abruptly, with some patients presenting with acute kidney injury (AKI) in emergency departments, clinical wards, or intensive care units.[3] The majority of AKI cases are attributed to drug therapy or renal hypoperfusion in hospitalized patients, which often requires continuous renal replacement therapies (CRRT). Regardless of the cause of acute or chronic renal impairment, these patients are at increased risk of accumulating drugs, toxic metabolites, and other nephrotoxins. For any drug that relies extensively on the kidney for elimination from the body (i.e., renal clearance > 30% of total clearance) and drug concentrations in blood or plasma are clearly associated with a pharmacodynamic effect (success, failure, or toxicity), dose adjustments are necessary when renal function is considerably reduced. The aim of this chapter is to describe dosing strategies for patients with CKD, AKI, and those receiving renal replacement therapies on an intermittent and/or continuous basis.

CLINICAL ASSESSMENT OF KIDNEY FUNCTION

The indices of glomerular and tubular function most widely utilized clinically include daily urinary protein excretion rate (glomerular), urine albumin-creatinine ratio (glomerular), fractional excretion of sodium (tubular), and serum creatinine concentration (glomerular and tubular). Creatinine is excreted by glomerular filtration and tubular secretion, making creatinine clearance (CrCl) a composite index of renal function that has been strongly associated with the total and renal clearance of many drugs that are eliminated by the kidney and is the primary index of renal drug dosing in FDA product labeling.

In patients with CKD stages 1 through 5 (pre-dialysis), the Cockcroft-Gault (CG) equation (see Chapter 2) is commonly used to estimate CrCl in the presence of stable kidney function. Newer equations that estimate GFR (eGFR), such as the CKD-EPI equations, are most appropriately used for identifying CKD and staging their degree of CKD severity.[4] Although the Modification of Diet in Renal Disease (MDRD) equation was initially adopted into automated systems for reporting GFR in clinical settings, it has been shown to be largely inaccurate at GFR > 60 mL/min and has since been replaced by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Neither of these eGFR equations has been consistently demonstrated to be equivalent to CG or measured CrCl when adjusting drug doses for renal impairment.[5,6] Recent studies by the Food and Drug Administration (FDA) and others showed that eGFR equations yield significantly higher estimates of kidney function, and significantly different dose calculations, when compared to CG equation, particularly in elderly individuals and those receiving narrow therapeutic index drugs such as enoxaparin.[5-9] Thus, renal dosing practices should remain consistent with the original pharmacokinetic studies of a particular drug in CKD, which to date generally involves estimation of CrCl.

Quantification of renal function in patients with AKI, where renal function and serum creatinine values are rapidly changing, is a challenging situation. Here, numerous equations for estimating CrCl based on two non-steady-state serum creatinine values have been proposed. See Chapter 2 for further discussions of appropriate use of equations to quantify renal function in various situations and patient populations. For critically ill patients with AKI receiving CRRT, estimation of both residual renal function (CrCl) and CRRT clearance are required for dose individualization (see section on dosing strategies).[10,11]

MECHANISMS OF DRUG CLEARANCE

Renal elimination

The process of renal drug elimination is a composite of glomerular and tubular functions, with the amount of drug cleared by the kidney (A_c) described by the following equation:

$$A_c = A_{filt} + A_{sec} - A_{reabs} \quad \textbf{(Eq. 1)}$$

Initially, unbound drug is filtered through the glomerulus (A_{filt}) into the proximal tubular fluid. When in the tubule, filtered drug may then be passively or actively reabsorbed (A_{reabs}) back into the bloodstream. This reabsorptive process is rare and occurs primarily in distal segments for unionized drugs at low urine flow rates. Drugs may also undergo active tubular secretion (A_{sec}), where unbound drug in plasma is transported into the tubular cell. This process of secreting drugs into the urine is mediated by transporters such as the organic anionic transporter (OAT), organic cationic transporter (OCT), or p-glycoprotein (P-GP). These transporters act in an efflux and uptake manner and are located along the basolateral and apical membranes of the proximal tubule.[12-14] The pathways work together to form an extremely efficient process of detoxification, resulting in renal clearance values that can exceed GFR, and in some cases approach renal plasma flow, which can be observed with para-aminohippurate and several penicillins. As filtration capacity (measured as GFR) progressively diminishes in CKD, some experimental data suggest that tubular secretory mechanisms may maintain their functionality, thereby providing significant renal clearance for some drugs even in the presence of severe glomerular damage.[15]

Kidney diseases can affect both glomerular and tubular function, leading to reduced overall drug elimination. As destruction of nephrons progresses, it has traditionally been believed that the function of all segments of the remaining nephrons is affected equally.[16] Based on this assumption, the rate of drug excretion in the normal or diseased kidney can be estimated by GFR or CrCl, which are predominantly measures of glomerular function.[17] The total renal clearance of a drug from the body also depends on (1) the fraction of the drug eliminated unchanged by the normal kidney, (2) the renal mechanisms involved in drug elimination, and (3) the degree of functional impairment of each of these pathways. The fraction of unchanged drug eliminated renally (f_e) and an assessment of the relationship between renal function and the drug's parameters, such as half-life (t½), total clearance (CL), and renal clearance (CL_{Renal}), can be used to individualize drug therapy. Ideally, renal drug clearance is determined by quantifying the amount of drug excreted in urine relative to the area under plasma drug concentration versus time curve (AUC) of drug in plasma, and renal function is measured using a GFR method such as iohexol or iothalamate clearance.[18] More commonly, the relationship between CrCl and drug clearance (CL) is evaluated in a large patient population with varying renal function, as follows:

$$CL = (A \times CrCl) + B \quad \textbf{(Eq. 2)}$$

$$k = (A \times CrCl) + B \quad \textbf{(Eq. 3)}$$

where A is the slope of the linear relationship between CrCl and either CL or k (the elimination rate constant), and B is the nonrenal CL (CL_{NR}) or nonrenal k (k_{NR}), respectively. This drug-specific information can then be used to design dose adjustment strategies in patients with renal insufficiency to minimize drug toxicity and optimize therapeutic efficacy.

Role of renal drug transporters

All aspects of drug transport in the kidney may be affected by co-administration of other substances, even in patients with normal renal function. First, drugs that cause a change in GFR will alter the CL_R of other renally eliminated drugs, assuming that tubular function remains unchanged. Second, substances may alter the tubular transport of one or more secretory pathways at uptake and efflux sites, such P-GP, OAT, or OCT, through noncompetitive inhibition or degradation of transport carriers. The most common type of tubular transport interaction occurs when two substances compete for tubular secretion by the same pathway. Clinically significant drug interactions involving renal transport mechanisms, both beneficial and detrimental, have been reported for the OAT, OCT, P-GP, and multi-drug and toxin extrusion (MATE) transporters (**Table 3-1**).[14]

TABLE 3-1. EXAMPLES OF RENAL DRUG TRANSPORTER-INTERACTION STUDIES IN HUMANS[14,19-23]

Transporter(s) (Gene)	Substrate	Inhibitor	Pharmacokinetic Results
P-GP (ABCB1)	Fexofenadine	Probenecid	44%↓ CL/F; 70%↓ CLR; 53%↑ AUC
	Cimetidine	Itraconazole	26%↓ CL; 30%↓ CLR; 25%↑ AUC[66]
	Digoxin	Itraconazole	21%↓ CLR; 50%↑ AUC
	Digoxin	Ritonavir	42%↓ CL/F; 21%↓ CLR; 86%↑ AUC
OAT1 (SLC22A6)/ OAT4 (SLC22A11)	Zidovudine	Probenecid	49%↓ CL; 56%↓ CLR; 50%↑ T1/2
	Ciprofloxacin	Probenecid	41%↓ CL; 64%↓ CLR; 74%↑ AUC
OAT3 (SLC22A8)	Benzylpenicillin	Probenecid	78%↓ CLR; 327%↑ AUC
OCT1 (SLC22A1)	Metformin	Cimetidine[a]	50%↓ CL/F; 50%↓ CLR; 57%↑ AUC 37%↓ CL/F; 17%↑ AUC
OCT2 (SLC22A2)	Amantadine	Quinidine	33%↓ CLR
MATE1 (SLC47A1)	Pramipexole	Cimetidine	57%↑ AUC; 40%↑ T1/2

[a]Interaction observed only in patients with OCT1 GG genotype.

MATE = multi-drug and toxin extrusion protein, OAT1/4 = family of organic anion transporters 1–4, OCT1 = organic cation transporter 1, OCT2 = organic cation transporter 2, P-GP = p-glycoprotein.

Although the mechanism is not well defined, an interaction between cimetidine and creatinine has been reported.[14] Cimetidine appears to block the OCT, P-GP, or MATE-mediated tubular secretion of creatinine, which then provides for a more accurate assessment of the GFR using a CrCl estimation method. There is increasing evidence to suggest that genetic variability of renal drug transporters, such as OAT1 and OCT1, may be an important determinant of urinary drug excretion. Other transporters such as the peptide transporter and concentrative nucleoside transporters may also contribute to renal drug elimination of drugs such as β-lactam antibiotics and didanosine, respectively.

An example of the beneficial effect of renal interactions is the management of drug toxicity by enhancing urinary excretion of the toxin to reduce serum drug concentrations, or by inhibiting drug uptake in tubules. For example, administration of urinary acidifying agents such as ammonium chloride, reduces the renal tubular reabsorption of weak basic drugs such as xanthines, amphetamine, and phenobarbital, resulting in increased renal elimination. In contrast, urinary alkalinizing agents would reduce the renal elimination of weak basic drugs, which enhances systemic exposure. A known mechanism of cidofovir nephrotoxicity is intracellular localization of the drug in the proximal tubule. The use of probenecid to block cellular uptake of cidofovir provides renal protection, thereby circumventing the development of nephrotoxicity caused by this agent.

NONRENAL MECHANISMS

Metabolism

Biotransformation of drugs by Phase I (oxidative) and Phase 2 (conjugation) reactions generally results in the formation of inactive metabolic products. Decreased intra-renal metabolism, decreased hepatic metabolism, and reduced renal clearance of active or toxic metabolites have all been noted in CKD and may result in significant reductions in drug elimination (**Table 3-2**).[24-27] The kidney itself plays an important role in the metabolism of many endogenous proteins and small peptides in addition to some drugs. For example, renal dehydropeptidase I, located in high concentrations along the brush border of the nephron inactivates the carbapenem antibiotic imipenem.[28] Data from animal models of CKD and evidence in ESKD patients have shown that hepatic CYP activity is reduced by up to 30% in the presence of renal failure, which can significantly impact drug clearance.[29-30] For example, the nonrenal clearance of reboxetine, which is extensively metabolized by CYP3A and minimally excreted unchanged by the kidneys, was 30% lower in ESKD patients (CKD stage 5) compared to those with mild renal impairment (CKD stage 2–3), and 67% lower than subjects with normal renal function.[31] Altered stereoselective metabolism may also occur in CKD. For example, a preferential increase in formation of metoprolol R-MAM and OHM was observed in CKD patients relative to normal controls.[32] Thus, for drugs where nonrenal clearance is affected by renal disease, appropriate dose adjustments and close monitoring is needed to maintain steady state drug concentrations at values similar to individuals with normal renal and hepatic function.

TABLE 3-2. DRUGS REPORTED TO HAVE REDUCED NONRENAL CLEARANCE IN CKD

Acyclovir[a]	Cyclophosphamide[c]	Nitrendipine[b]
Aztreonam[a]	Didanosine[a]	Nortriptyline[c]
Bufurolol[b]	Encainide[b]	Oxprenolol[b]
Bupropion[c]	Erythromycin[c]	Procainamide[c]
Captopril[c]	Felbamate[c]	Propoxyphene[b,c]
Carvedilol[c]	Guanadrel[b]	Propranolol[c]
Cefepime[a]	Imipenem[a]	Quinapril[a]
Cefmetazole[a]	Isoniazid[c]	Raboxetine[b]
Cefonicid[a]	Ketoprofen[a]	Raloxifene[c]
Cefotaxime[a]	Ketorolac[a]	Repaglinide[c]
Ceftibuten[a]	Lidocaine[c]	Rosuvastatin[a]
Ceftriaxone[a]	Lomefloxacin[a]	Roxithromycin[b]
Cerivastatin[b]	Losartan[c]	Simvastatin[c]
Cibenzoline[b]	Lovastatin[c]	Sparfloxacin[a]
Cilastatin[a]	Metoclopramide[a]	Telithromycin[a]
Cimetidine[a]	Minoxidil[c]	Valsartan[c]
Ciprofloxacin[a]	Morphine[c]	Vancomycin[a]
Codeine[c]	Nicardipine[c]	Verapamil[c]
	Nimodipine[c]	Zidovudine[a]

[a]Indicates that a renal dose adjustment is required; see Table 3-3 or package insert.
[b]Indicates drug not available in United States.
[c]Indicates no FDA-approved dose adjustment in CKD provided; use with caution in CKD.

Gastrointestinal absorption

The effect of CKD on gastrointestinal GI absorption of drugs is not well understood and the impact of AKI on GI absorption is unknown. Many patients with diabetes mellitus are known to have decreased gastric emptying; therefore, delayed absorption of some drugs can be expected in the presence of diabetes.

However, the extent of absorption and overall bioavailability are typically unchanged compared to patients without renal disease. Although the bioavailability of a few drugs are reportedly reduced, consistent findings of impaired absorption in CKD patients is lacking. For the majority of drugs that have been evaluated, GI absorption is either unchanged or increased, suggesting that pre-systemic (or first-pass) extraction may be reduced in these patients. The absorption of some drugs such as digoxin, doxycycline, levothyroxine, and fluoroquinolone antibiotics may be impaired due to the concomitant administration of phosphate binders, including sucroferric oxyhydroxide, that are commonly observed in CKD patients.[33-35]

VOLUME OF DISTRIBUTION

The volume of distribution (V) of many drugs, including aminoglycosides and cephalosporins, has been reported to be significantly increased in CKD patients.[36-38] Proposed mechanisms of increased V for various drugs include fluid overload, decreased plasma protein binding due to hypoalbuminemia or competitive binding interactions with uremic toxins, or altered tissue binding. Decreased V in patients with ESRD is rare and, if present, is due to reduced binding to tissue proteins. The two primary plasma proteins that bind acidic and basic drugs are albumin and α_1-acid glycoprotein (AAG), respectively. The protein binding for some acidic drugs such as penicillins, cephalosporins, furosemide, theophylline, and phenytoin, is reduced in patients with renal failure.[39,40] The binding of basic drugs to AAG is, however, generally unaltered in CKD patients, although increased V has been reported for some drugs such as bepridil and disopyramide.[41,42] Although changes in plasma protein binding are not usually clinically significant, close monitoring in patients receiving narrow therapeutic index drugs is warranted unless there is clinical confirmation of no associated problem.

DRUG DOSING STRATEGIES FOR CKD PATIENTS

For drugs that rely to a significant degree on the kidneys for total body elimination (i.e., fe > 0.3), dose reductions may be required in patients with CKD to avoid systemic accumulation and adverse drug events. In nearly all cases, the FDA-approved drug product label (i.e., package insert) includes drug dose adjustment guidelines based on the degree of reduction in CrCl.[43]

It is important to understand the mathematical basis for dose adjustment recommendations. The following approach involves an initial estimation of the drug's CL (or k) based on either literature data or derivation of a regression equation from clinical trial data.[17,44] The next step is to use the estimates of CL or k to determine the dose adjustment factor (Q):

$$Q = k_R \div k_{norm} \quad \textbf{(Eq. 4)}$$

$$Q = CL_R \div CL_{norm} \quad \textbf{(Eq. 5)}$$

R = in reduced renal function
norm = in normal renal function

An assumption when using Equation 4 is that V does not change in the presence of renal disease and, for both equations, that the normal values are representative of individuals with CrCl ≥ 120 mL/min.

An alternative approach to calculating Q involves determination of the ratio (KF) of the patient's CrCl to a presumed normal CrCl of 120 mL/min, based on estimation of the fraction of drug eliminated unchanged renally in subjects with normal renal function (f_e), as:

$$Q = 1 - [fe\ (1 - KF)] \quad \textbf{(Eq. 6)}$$

Use of this approach is based on the following assumptions:

- elimination of the drug is best described by a linear, first-order process;
- glomerular and tubular function decrease in a parallel fashion in all renal diseases;
- other aspects of drug absorption (bioavailability), distribution (protein binding) and metabolism (nonrenal clearance) remain constant;

- metabolites of the drug are pharmacologically inactive or do not accumulate in renal disease; and
- the pharmacodynamics (i.e., the concentration or dose response relationship) of the drug or metabolites remains unchanged by renal disease.[17,43]

Once the dosage adjustment factor (Q) for the patient has been estimated, the dosage regimen for that drug can be modified to achieve the desired serum concentration profile. If clinically significant relationships between peak and trough concentrations and efficacy or toxicity have been described then the dosage regimen should be designed to attain and maintain these target values. In all other cases, the goal of dose individualization may be to achieve similar average steady state concentrations (Css_{av}) to those typically observed in patients with normal renal function. If the goal is to maintain the same Css_{av} and the dosage form precludes modification (e.g., time-release capsule), then one must prolong the dosing interval (τ). Conversely, if the standard dosing interval is desired, the dose can be reduced to maintain the desired Css_{av}. The new dosing interval (τ_R) or dose (D_R) for the patient with renal insufficiency can be calculated from the interval (τ_{norm}) and dose (D_{norm}) used in normal renal function as follows:

$$\tau_R = \tau_{norm} \div Q \qquad \textbf{(Eq. 7)}$$

$$D_R = D_{norm} \times Q \qquad \textbf{(Eq. 8)}$$

The strategies shown in Eq. 7 and 8 are designed to achieve the same Css_{av}. However, the resultant steady state peak [Css_{max}] and trough [Css_{min}] concentrations may be markedly different in each case. The reduced dosage strategy (Eq. 8) yields lower Css_{max} and higher Css_{min} compared to the prolonged dosage interval (Eq. 7) approach, which results in values that are similar to the individual with normal renal function. If this approach yields an interval that is impractical, a new dose can be calculated using a fixed, pre-specified dose interval (τ_R), as follows:

$$D_R = [\, D_{norm} \times Q \times \tau_R] \,/\, \tau_{norm} \qquad \textbf{(Eq. 9)}$$

The methods of dosage individualization described above (Eq. 7–9) are applicable to clinical settings where no serum concentration data are available to guide the therapeutic decision making process. These approaches are based on data obtained from clinical pharmacokinetic studies in patients with renal impairment, and serve as the basis for making initial dosing decisions based on renal function (CrCl) as shown in **Table 3-3**. However, when a specific serum concentration-time profile, peak, trough, or AUC is required, measurement of drug concentrations and traditional therapeutic drug monitoring approaches are recommended (see the drug-specific chapters of this book).

TABLE 3-3. PHARMACOKINETIC PARAMETERS AND MAINTENANCE DOSAGES FOR SOME COMMONLY USED DRUGS IN PATIENTS WITH CKD[46-49,a]

			CrCl (mL/min)			
Drug	**V (L/kg)**	**fe**	**120–70**	**70–50**	**50–10**	**<10**
Acyclovir	0.7	0.40–0.70	5 mg/kg every 8 hr	5 mg/kg every 8 hr	5 mg/kg every 12–24 hr	2.5 mg/kg every 24 hr
Amantadine	4–5	0.90	100 mg every 12 hr	Every 24–48 hr	Every 48–72 hr	Every 7 d
Amphotericin B	4	0.05–0.10	20–50 mg every 24 hr	Every 24 hr	Every 24 hr	Every 24–36 hr
Amoxicillin	0.26	0.50–0.70	250–500 mg every 8 hr	Every 8 hr	Every 8 hr–12 hr	Every 24 hr
Ampicillin	0.17	0.30–0.90	250 mg–2 g every 6 hr	Every 6 hr	Every 6–12 hr	Every 12–24 hr
Apixaban	0.3	0.27	5 mg every 12 hr	100%	50%	Not recommended

TABLE 3-3. CONTINUED

			CrCl (mL/min)			
Drug	**V (L/kg)**	**fe**	**120–70**	**70–50**	**50–10**	**<10**
Atenolol	1.1	0.90	50–100 mg every 24 hr	100% every 24 hr	50% every 48 hr	30%–50% every 96 hr
Aztreonam	0.5–1	0.75	2 g every 8 hr	100%	50%–75%	25%
Benazepril	0.15	0.20	10 mg every 24 hr	100%	50%–75%	25%–50%
Bisoprolol	3	0.50	10 mg every 24 hr	100%	75%	50%
Cefazolin	0.13–0.22	0.75–0.95	1–2 g every 8 hr	Every 8 hr	50% every 12 hr	50% every 18–24 hr
Cefepime	0.3	0.85	2 g every 8–12 hr	Every 12–24 hr	Every 12–24 hr + dose reduction	Every 24 hr + dose reduction
Cefotaxime	0.15–0.55	0.60	1 g every 6 hr	Every 6 hr	Every 8–12 h	Every 24 hr
Cefoxitin	0.2	0.80	1–2 g every 8 hr	Every 8 hr	Every 8–12 hr	Every 24–48 hr
Ceftazidime	0.28–0.4	0.60–0.85	1–2 g every 8 hr	Every 8–12 hr	Every 24–48 hr	Every 48 hr
Cefteroline	0.37	0.64	600 mg every 12 hr	600 mg every 12 hr	50%–66%	33%
Ceftolozane/tazobactam	0.19 (C) 0.25 (T)	0.95 (C) 0.80 (T)	1.5 g every 8 hr	100%	25%–50%	750 mg × 1 then 150 mg every 8 hr
Cefuroxime IV	0.13–1.8	0.90	0.75–1.5 g every 8 hr	Every 8 hr	Every 8–12 hr	Every 24 hr
Cephalexin	0.35	0.98	250–500 mg every 6 hr	Every 8 hr	Every 12 hr	Every 12 hr
Cetirizine	0.4–0.6	0.60–0.70	5–20 mg every 24 hr	100%	50%	25%
Cimetidine	0.8–1.3	0.50–0.70	400 mg every 12 hr	100%	50%	25%
Cidofovir	0.3–0.8	0.90	5 mg/kg every 1–2 wk	100%	Avoid	Avoid
Ciprofloxacin IV	2.5	0.50–0.70	400 mg every 12 hr	100%	50%–75%	50%
Clarithromycin	2–4	0.15–0.25	0.5–1 g every 12 hr	100%	75%	50%–75%
Daptomycin	0.1	0.78	6 mg/kg every 24 hr	100%	50%–100%	50%
Didanosine	1	0.40–0.69	200 mg every 12 hr (125 mg if < 60 kg)	100%	150–200 mg every 24 hr (100–150 mg if <60 kg)	50% every 24 hr 75 mg if <60 kg
Doripenem	0.24	0.70	500 mg every 8 hr	100%	33%–50%	33%
Enalapril	No data	0.43	5–10 mg every 12 hr	100%	75%–100%	50%
Famciclovir	1.5	0.50–0.65	500 mg every 8 hr	100%	250–500 mg every 24–48 hr	250 mg every 48 hr
Famotidine	0.8–1.4	0.65–0.80	20–40 mg every 24 hr	50%	25%	10%
Fexofenadine	5–6	0.10	60 mg every 12 hr	Every 12 hr	Every 12–24 hr	Every 24 hr
Flucytosine	0.6	0.90	37.5 mg/kg every 6 hr	Every 12 hr	Every 16 hr	Every 24 hr

TABLE 3-3. CONTINUED

			CrCl (mL/min)			
Drug	**V (L/kg)**	**fe**	**120–70**	**70–50**	**50–10**	**<10**
Foscarnet	0.3–0.6	0.85	40 mg/kg every 8 hr	28 mg/kg	15 mg/kg	6 mg/kg
Gabapentin	0.7	0.90	300–600 mg every 8 hr	400 mg every 8 hr	300 mg every 12–24 hr	300 mg every 48 hr
Ganciclovir	0.47	0.90–1.0	5 mg/kg every 12 hr	Every 12 hr	Every 24–48 hr	Every 48–96 hr
Glipizide	0.13–0.16	0.05–0.07	2.5–15 mg every 24 hr	100%	50%	50%
Glyburide	0.2–0.3	0.50	1.25–20 mg every 24 hr	No data	Avoid	Avoid
Insulin	0.15	None	Variable	100%	75%	50%
Insulin (Lispro)	0.26–0.36	No data	Variable	100%	75%	50%
Itraconazole	10	0.35	100–200 mg every 12 hr	100%	100%	50%
Lamivudine	0.83	0.70–0.80	150 mg every 12 hr	100% every 24 hr	50–150 mg every 24 hr	25–50 mg every 24 hr
Levetiracetam	0.5–0.7	0.66	0.5–1.5 g every 12 hr	0.5–1 g every 12 hr	250–750 mg every 12 hr	0.5–1 g every 24 hr
Levofloxacin	1.1–1.5	0.67–0.87	500 mg every 24 hr	100%	250 mg every 24–48 hr	250 mg every 48 hr
Linezolid	0.57-0.71	0.30	600 mg every 12 hr	100%	100%	100%
Lisinopril	0.13–0.15	0.80–0.90	5–10 mg every 24 hr	100%	50%–75%	25%–50%
Meropenem	0.35	0.65	0.5–1 g every 6 hr	500 mg every 6 hr	250–500 mg every 12 hr	250–500 mg every 24 hr
Metformin[b]	1–4	0.90–1.0	500–850 mg every 12 hr	50%[b]	25% (avoid)[b]	Avoid[b]
Methicillin	0.31	0.25–0.80	1–2 g every 4h	Every 4–6 hr	Every 6–8 hr	Every 8–12 hr
Metoclopramide	2–3.4	0.10–0.22	10–15 mg every 6 hr	100%	75%	50%
Metronidazole	0.3–0.9	0.20	7.5 mg/kg every 6 hr	100%	100%	50%
Nizatidine	0.8–1.3	0.10–0.15	150–300 mg every 24 hr	75%	50%	25%
Olmesartan	0.24	0.50	20 mg every 24 hr	100%	Use caution when CrCl < 20 mL/min	Use caution when CrCl < 20 mL/min
Oxcarbazepine[c]	0.7–0.8	0.30	300–600 mg every 12 hr	100%	75%	50%
Penicillin G	0.3–0.4	0.60–0.85	0.5–4 MU every 6 hr	100%	75%	20%–50%
Pentamidine	3–4	0.05	4 mg/kg every 24 hr	Every 24 hr	Every 24 hr	Every 24–36 hr
Piperacillin	0.2–0.3	0.75–0.90	3–4 g every 4 hr	Every 4–6 hr	Every 6–8 hr	Every 8 hr
Quinapril	1.5	0.30	10–20 mg every 24 hr	100%	75%–100%	75%
Ramipril	1.2	0.1–0.21	10–20 mg every 24 hr	100%	50%–75%	25%–50%

TABLE 3-3. CONTINUED

			CrCl (mL/min)			
Drug	**V (L/kg)**	**fe**	**120–70**	**70–50**	**50–10**	**<10**
Ranitidine	1.2–1.8	0.80	150–300 mg every 24 hr	75%	50%	25%
Rivaroxaban	0.71	0.36	15-20 mg every 24 hr	100%	75% (avoid if CrCl < 30 mL/min)	Not recommended
Sotalol	1.3	0.60	160 mg every 24 hr	100%	30%	15%–30%
Spironolactone	No data	0.20–0.30	25 mg every 6–8 hr	Every 6–12 hr	Every 12–24 hr	Avoid
Stavudine	0.5	0.40	30–40 mg every 12 hr	100%	50% every 12–24 hr	50% every 24 hr
Tedizolid	0.96-1.14	<0.03	200 mg every 24 hr	100%	100%	100%
Tetracycline	0.7	0.48–0.60	250–500 mg every 6 hr	Every 8–12 hr	Every 12–24 hr	Every 24 hr
Tigecycline	7-9	0.22	50 mg every 12 hr	100%	100%	100%
Topiramate	0.6–0.8	0.70–0.97	200 mg every 12 hr	100%	50%	25%
Trimethoprim	1–2.2	0.40–0.70	100–200 mg every 12 hr	Every 12 hr	Every 18 hr	Every 24 hr
Venlafaxine	6–7	0.05	75–375 mg every 24 hr	75%	50%	50%
Vigabatrin	0.8	0.70	1–2 g every 12 hr	Every 24 hr	Every 48 hr	Every 2–3d

[a]The doses provided are approximations due to overlap in CrCl ranges for each drug. See the FDA approved product label for updates and specific dose recommendations for drugs listed in this table.

[b]Contraindicated in patients with an eGFR below 30 mL/min/1.73 m^2. Starting metformin in patients with an eGFR between 30 and 45 mL/min/1.73 m^2 is not recommended. In patients taking metformin whose eGFR later falls below 45 mL/min/1.73 m^2, assess the benefits and risks of continuing treatment. Discontinue metformin if the patient's eGFR later falls below 30 mL/min/1.73 m^2.

[c]MHD, the monohydroxy derivative, is the active metabolite 10,11-dihydro-10-hydroxy-carbazepine (monohydroxy derivative, MHD).

fe = fraction excreted unchanged in the urine, GFR = glomerular filtration rate (the range following GFR indicates the use of the dose that corresponds to that range of GFR in patients not on dialysis), MU = million units, PB = plasma protein binding, V = volume of distribution.

The doses provided are approximations due to overlap in CrCl ranges for each drug. See the FDA approved product label for updates and specific dose recommendations.

HEMODIALYSIS AND CONTINUOUS RENAL REPLACEMENT THERAPY

HD is the predominant modality of renal replacement therapy for over 500,000 individuals who reside in the United States.[1] The medical care environment of free-standing community-centered dialysis units often places them outside of traditional healthcare institutions and, because only a small number of pharmacists practice in this setting, pharmacotherapeutic patient care management is often dependent on the nursing staff. The medication burden of typical HD-dependent patients is extensive: they often are prescribed 12 or more medications and also consume multiple over-the-counter drugs and dietary supplements.[45] Therefore, it is essential for community pharmacists to recognize the influence of HD on the pharmacokinetics and dynamics of the medications that these patients are receiving. The establishment of a consultant relationship with dialysis centers is one avenue for a pharmacist to participate in the care of these vulnerable patients, just as many pharmacists do for those who reside in skilled nursing facilities.[50] Finally, because the average age of HD patients is over 65 and they have a significant medication burden, they are prime candidates for the receipt of comprehensive medication reviews as part of the Medicare Part D Medication Therapy Management Program.

This section of the chapter serves as a primer on the impact of renal replacement therapies such as HD and CRRTs on acute and chronic drug therapy regimens and provides clinically useful dosage recommendations for many of the most commonly used medications for this patient population.

Principles of hemodialysis

The removal of a drug by dialysis is dependent on several factors, including the physiochemical and pharmacokinetic characteristics of the drug, the patient's residual renal function, volume status and acuity of their illness, a myriad of other factors mentioned in the preceding section, and finally the dialysis prescription, which consists of the selection of the dialyzer, the blood and dialysate flow rates, the extent of fluid removal, and the frequency and duration of the procedure.[51-53] Drugs that are highly protein bound have low dialysis clearances because α_1-acid glycoprotein and albumin have molecular weights in excess of 20,000 Daltons (D) and, thus, do not cross the dialysis membrane. Drugs that have a V greater than 2 L/kg are also poorly removed by HD. **Table 3-4** outlines the key factors.

TABLE 3-4. FACTORS AFFECTING THE HEMODIALYZABILITY OF A DRUG

		Impact on Dialyzability
Physicochemical and pharmacokinetic drug properties	Molecular weight < 10,000 Daltons	Increases
	High water solubility	Increases
	High lipid solubility	Decreases
	Increased ionization—anionic	Decreases
	Large volume of distribution	Decreases
	High protein binding	Decreases
	Lower red blood cell partition	Decreases
Mechanical properties of the renal replacement therapy	Larger surface area of dialyzer	Increases
	Higher porosity dialysis membrane	Increases
	Higher dialysate flow rates	Increases
	Higher blood flow rate	Increases

The degree of drug removal by the HD procedure, be it acute for the management of AKI or the typical three-times-a-week regimen for the management of stage 5 CKD, can be dramatically affected by the prescribed dialysis regimen.[51,53-55] The intensity of the HD prescription for patients who have stage 5 CKD has increased dramatically in the last decade, in part because of increasing blood and dialysate flow rates and the use of new high flux, large surface area, dialysis filters. Dialyzers composed of synthetic materials (e.g., polysulfone, polymethylmethacrylate, or polyacrylonitrile) readily remove drugs with molecular weights between 1,000 and 5,000 D, which in the past were likely to be considered non-dialyzable.[53,55] Thus, high-molecular-weight drugs such as vancomycin are now extensively cleared by HD. In addition, significant increases in HD clearance of 50%–100% have been noted for many drugs, especially antibacterial agents that have a molecular weight of less than 1,000 D.[53]

Dosage regimen adjustment strategies for patients receiving hemodialysis

Prospective individualization of drug dosage regimens is recommended for narrow therapeutic range drugs, such as the aminoglycosides, vancomycin, and the multiple others identified in this chapter. Several factors contribute to the complexity of accomplishing this in the CKD patient who is receiving chronic HD. Of considerable importance is the long turnaround time associated with measurement and reporting of serum concentrations in the ambulatory care setting and the delay in implementing a new dosage. Thus, in most ambulatory HD care situations, patients will initially benefit from the

recognition that a drug dosage regimen should be adjusted and the implementation of a best practical dosage regimen based on data derived from prior clinical investigations. The data in the second column of Table 3-5 presents recommendations for dialysis-dependent CKD patients with a residual CrCl <10 mL/min who are receiving intermittent HD on a three times per week schedule. This is the rationale for the every 48–72 hr dosage intervals for many agents included in **Table 3-5**, because drug administration is almost always fixed to be during the last hour of or after the end of the dialysis procedure. These dosage regimens should be used with caution since there is tremendous variability in the clearance efficiency of the over 100 dialysis filters currently available.[58,59] Dosage recommendations for HD patients derived prior to 1995 likely provide an underestimate of patient needs because of the enhanced clearance with newer, more efficient, dialyzers and more aggressive dialysis prescriptions.

For medications that are commonly individualized on the basis of serum concentration guidance, the primary dosage regimen design issues are to avoid administration in the hours immediately before dialysis to minimize excessive removal of standard doses of the medication and the use of simple consistent administration schedules that minimize the need for variable drug doses being administered on non-dialysis as well as dialysis days. For some drugs, higher doses have been proposed and evaluated to facilitate delivery during dialysis that compensate for the enhanced removal resulting from administration during dialysis.[59,60] Although this approach may increase medication cost, it may enhance patient compliance and improve the efficiency of the dialysis center. The primary objective for most medications is to design a regimen for administration on dialysis days such that the dose given at the end of dialysis is sufficient to achieve the desired maximum drug concentration. In this setting, the dose to be administered after dialysis (D_{postHD}) can be calculated as:

$$D_{postHD} = V \times (C_{max} - C_{postHD}) \quad \textbf{(Eq. 10)}$$

$$C_{postHD} = C_{preHD} \times (e^{-kt} + e^{-kHDt}) \quad \textbf{(Eq. 11)}$$

where V is the patient's estimated volume of distribution for the drug of interest, e^{-kt} is the fraction of drug concentration (C_{preHD}) remaining at the end of the dialysis procedure as a result of the patient's residual total body clearance ($k_{pt} = CL_{pt} \div V$), and e^{-kHDt} is the fraction of drug concentration (C_{preHD}) remaining as a result of elimination by the dialyzer ($k_{HD} = CL_{HD} \div V$). The duration of the dialysis procedure in hours is expressed as t. Values for CL_{pt} can be derived from the drug clearance to renal function relationships in the literature or estimated from the information in Table 3-3, while CL_{HD} values for many dialyzers and dialysis procedures will need to be acquired from reliable literature sources.[51-53]

Alternatively CL_{HD} can be measured for individual patients if a series of serum concentrations are collected using the following approach[36]:

$$CL_{HD} = \left(\frac{C_{art} - C_{ven}}{C_{art}} \right) \times (Qb\,(1 - Hct))$$

Where C_{art} is the concentration of the drug in the plasma entering the dialyzer, C_{ven} is the concentration of the drug in the plasma leaving the dialyzer, Qb is the blood flow through the dialyzer, and Hct is the patient's hematocrit. This information can be used with the measured CL_{pt} using the equation to estimate k_{HD} described in the preceding paragraph to calculate the post HD dose (Eq. 10).

Dosage individualization strategies for patients receiving continuous renal replacement therapies

In contrast to intermittent HD, CRRTs that were developed over the past two decades have proven to be a viable management approach for hemodynamically unstable patients with or without AKI.[11] Several variants have been developed, and there are currently two primary techniques employed in most clinical settings Drug removal by continuous venovenous hemofiltration (CVVH) occurs by convection/ultrafiltration, whereas continuous venovenous hemodiafiltration (CVVHDF), which is more efficient, uses convection/ultrafiltration and diffusion as the two predominant means for drug removal.

Optimization of drug therapy for patients with AKI is often quite challenging. Interpretation of the limited literature available on drug removal by CRRT in critically ill patients is complicated by the large variation between hemofilters, the CRRT prescription, and the marked degree of interpatient variability in residual renal function and fluid volume status.[61,62] This is further challenged by the lack of consistent reporting of CRRT studies in new drug applications submitted to the FDA.[63] The essential elements that characterize each of the predominant CRRT variants are well described elsewhere.[64,65]

Although dosing guidelines based on data derived from *in vitro* experiments or studies in patients with stable stage 5 CKD may not reflect the clearance and V in critically ill AKI patients, this may be the only information available for many drugs. Table 3-5 presents drug dosage recommendations for AKI patients with a CrCl <10 mL/min who are receiving CVVH or CVVHDF compiled from many sources.[56,57,61,62,65] These recommendations differ from FDA-approved product labeling in those situations where more current clinical information was available in the literature.

TABLE 3-5. DOSAGE RECOMMENDATIONS FOR PATIENTS RECEIVING HEMODIALYSIS, CVVH, OR CVVHDF[a]

	Dosage Recommendation[a]		
Drug	**HD**	**CVVH**	**CVVHDF**
Acyclovir	2.5–5 mg/kg every 24 hr	5–10 mg/kg every 24 hr	5–10 mg/kg every 12–24 hr
Amantadine	200 mg every 7 days	100 mg every 24–48 hr	100 mg every 24–48 hr
Amphotericin B	0.25–1.5 mg/kg every 24 hr	0.25–1.5 mg/kg every 24 hr	0.25–1.5 mg/kg every 24 hr
Amoxicillin	250–500 every 24 hr	ND	ND
Amikacin	IND or 5–7.5 mg/kg every 48–72 hr	IND or 7.5 mg/kg every 24–48 hr	IND or 7.5 mg/kg every 24–48 hr
Ampicillin	1 g every 12 hr	1–2 g every 8–12 hr	1–2 g every 6–8 hr
Ampicillin/sulbactam	1.5–3 g every 12–24 hr	1.5–3 g every 8–12 hr	1.5–3 g every 6–8 hr
Atenolol	25–50 mg every 48–72 hr	25–50 mg every 24 hr	25–50 mg every 24 hr
Aztreonam	0.5 g every 12 hr	1–2 g every 12 hr	2 g every 12 hr
Benazepril	2.5–10 mg every 12–24 hr	5–20 mg every 12–24 hr	5–20 mg every 12–24 hr
Bisoprolol	2.5–10 mg every 24 hr	5–15 mg every 24 hr	5–15 mg every 24 hr
Cefazolin	15–20 mg/kg every 48–72 hr	1–2 g every 12 hr	2 g every 12 hr
Cefepime	1–2 g every 48–72 hr	1–2 g every 12 hr	2 g every 12 hr
Ceftazidime	1 g every 24 hr	1–2 g every 12 hr	2 g every 12 hr
Ceftaroline	200 mg every 12 hr	300 mg every 12 hr	300 mg every 12 hr
Ceftriaxone	1–2 g every 24 hr	1–2 g every 12–24 hr	1–2 g every 12–24 hr
Cephalexin	250–500 every 24 hr	ND	ND
Cidofovir	AVOID	2 mg/kg every 7 days	2 mg/kg every 7 days
Cimetidine	300 every 8–12 hr	200 every 12 hr	200 every 12 hr
Ciprofloxacin	0.2–0.4 g every 24 hr	0.2–0.4 g every 12–24 hr	0.4 g every 12 hr
Clarithromycin	Dose after HD	250–500 mg every 12 hr	250–500 mg every 12 hr
Colistin	1.5 mg/kg every 24–48 hr	2.5 mg/kg every 48 hr	2.5 mg/kg every 48 hr
Daptomycin	4–6 mg/kg every 48–72 hr	4 mg/kg every 24 hr	4 mg/kg every 24 hr
Didanosine	100 mg every 24 hr	200 mg every 12 hr	200 mg every 12 hr
Enalapril	5–10 mg every 24 hr	5–10 mg every 12–24 hr	5–10 mg every 12–24 hr
Famciclovir	250 mg after HD	500 mg every 12 hr	500 mg every 12 hr
Famotidine	5 mg every 24 hr	5–10 mg every 24 hr	5–10 mg every 24 hr
Fexofenadine	30 mg every 24 hr	60 mg every 24 hr	60 mg every 24 hr
Fluconazole	0.2–0.4 g every 48–72 hr	0.2–0.4 g every 24 hr	0.8 g every 24 hr

TABLE 3-5. CONTINUED

	Dosage Recommendation		
Drug	**HD**	**CVVH**	**CVVHDF**
Foscarnet	45–60 mg/kg every 48–72 hr after HD	60–80 mg/kg every 48 hr	60–80 mg/kg every 48 hr
Gabapentin	200–300 mg every 48–72 hr	300 mg every 12–24 hr	300 mg every 12–24 hr
Ganciclovir	0.625 (maintenance) to 1.25 (induction) mg/kg every 48–72 hr	1.25 mg/kg every 24 hr	2.5 mg/kg every 24 hr
Gentamicin	IND or 1.5–2 mg/kg every 48–72 hr	IND or 1.5–2 mg/kg every 24–48 hr	IND or 1.5–2 mg/kg every 24–48 hr
Glipizide	1.25–7.5 mg every 24 hr	1.25–7.5 mg every 24 hr	1.25–7.5 mg every 24 hr
Imipenem/ cilastatin	0.25–0.5 g every 12 hr	0.5 g every 8 hr	0.5 g every 6 hr
Lamivudine	1 mg/kg every 24 hr	4 mg/kg every 24 hr	4 mg/kg every 24 hr
Levetiracetam	500–750 every 24 hr	250–750 every 12 hr	250–750 every 12 hr
Levofloxacin	250–500 every 48–72 hr	500 every 24 hr	500 every 24 hr
Linezolid	600 mg every 12 hr	600 mg every 12 hr	600 mg every 12 hr
Meropenem	500 mg every 24 hr	0.5–1 g every 12 hr	0.5–1 g every 8–12 hr
Metformin	AVOID	AVOID	AVOID
Metoclopramide	5 mg every 6 hr	5–10 mg every 6 hr	5–10 mg every 6 hr
Metronidazole	0.5 g every 8–12 hr	0.5 g every 6–12 hr	0.5 g every 6–12 hr
Moxifloxacin	0.4 g every 24 hr	0.4 g every 24 hr	0.4 g every 24 hr
Ofloxacin	100-200 mg after HD	300 mg every 24 hr	300 mg every 24 hr
Piperacillin	2 g every 8 h + 1g supplemental dose after HD	ND	ND
Piperacillin/ tazobactam	2.25 g every 8–12 hr	2.25–3.75 g every 6–8 hr	3.375 g every 6 hr
Quinapril	2.5 mg every 12–24 hr	2.5–5 mg every 12–24 hr	2.5–5 mg every 12–24 hr
Ramipril	1.25–2.5 mg every 24 hr	2.5–5 mg every 24 hr	2.5–5 mg every 24 hr
Ranitidine	75–150 mg every 24 hr	150 mg every 12–24 hr	150 mg every 12–24 hr
Stavudine	20 mg every 24 hr	40 mg every 12 hr	40 mg every 12 hr
Tetracycline	250–500 every 24 hr	ND	ND
Ticarcillin/ clavulanate	2 g every 12 hr	2 g every 6–8 hr	3.1 g every 6 hr
Tobramycin	IND or 1.5–2 mg/kg every 48–72 hr	IND or 1.5–2 mg/kg every 24–48 hr	IND or 1.5–2 mg/kg every 24–48 hr
Topiramate	50 mg every 12 hr	100 mg every 12 hr	100 mg every 12 hr
Trimethoprim/ sulfamethoxazole	5–15 mg/kg (TMP) every 48–72 hr	2.5–7.5 mg/kg (TMP) every 12 hr	2.5–7.5 mg/kg (TMP) every 12 hr
Vancomycin	IND or 7.5 mg/kg every 48–72 hr	IND or 10–15 mg/kg every 24–48 hr	IND or 7.5–10 mg/kg every 12 hr
Vigabatrin	1–2 g every 48–72 hr	1–2 g every 48 hr	1–2 g every 48 hr
Voriconazole[a]	4 mg/kg every 12 hr	4 mg/kg every 12 hr	4 mg/kg every 12 hr

[a]The amount of drug dialyzed can be highly dependent on conditions such as type of filter, blood filtration and ultrafiltration rates. Therefore, the adjustments in this table are estimates based on best available data. Refer to the FDA approved package insert for specific dose recommendations.

[b]Intravenous voriconazole should not be used in CKD (non-dialysis) due to accumulation of the vehicle (sulfobutylether-B-cyclodextrin, SBECD).

IND = individualize because desired concentrations and or pharmacodynamic endpoints may vary markedly, ND = no data available.

When there is a need to tightly control patient exposure to a given drug, either for the enhancement of therapeutic response or the minimization of risk of adverse events, the dosage regimen for patients receiving CRRT can be individually ascertained by adding the estimated or measured drug clearance by CRRT to the patient's residual drug clearance. Once the total clearance is known, the dosage regimen can be projected using the same principles as those described for patients with stable CKD. For example, the dosage regimen for cefepime of a patient receiving CVVHDF will be predicated on the sum of the patient's residual clearance and the clearance associated with CVVHDF, which can be approximated as follows. If a patient with a CrCl of 10 mL/min is receiving CVVHDF with an AN69 filter at blood, ultrafiltrate, and dialysate flow rates of 200, 12, and 33 mL/min, respectively, and is to receive cefepime while on CVVHDF, the patient's residual cefepime clearance (CL_{RES}) can be estimated using the following regression equation relating CrCl and cefepime clearance drawn from the literature.[36] The cefepime clearance of a patient with normal renal function (CrCl of 120 mL/min) would be calculated as:

$$CL_{norm}\ (mL/min) = [0.96 \times (CrCl)] + 10.9$$

$$CL_{norm} = [0.96 \times 120] + 10.9$$

$$CL_{norm} = 126.1\ mL/min$$

This patient's cefepime clearance as the result of his residual CrCl value can be calculated similarly:

$$CL_{RES}\ (mL/min) = [0.96 \times (10)] + 10.9$$

$$CL_{RES} = [0.96 \times (10)] + 10.9$$

$$CL_{RES} = 20.5\ mL/min$$

The total clearance while on CVVHDF would be the sum of the patient's residual clearance and the cefepime clearance associated with CVVHDF, which can be approximated as follows:

$$CL_{CVVHDF} = [(UFR + DFR) \times f_u)] \qquad \textbf{(Eq. 13)}$$

(where UFR = ultrafiltrate formation rate, DFR = dialysate flow rate, and fu = fraction unbound)

$$CL_{CVVHDF} = [(12 + 33) \times 0.97] = 43.7\ mL/min$$

$$CL_T = CL_{RES} + CL_{CVVHDF} \qquad \textbf{(Eq. 14)}$$

$$CL_T = 20.5\ mL/min + 43.7\ mL/min$$

$$CL_T = 64.2\ mL/min$$

The dosage adjustment factor would then be:

$$Q = CL_T / CL_{norm}$$

$$Q = 64.2 \div 126$$

$$Q = 0.51$$

For this patient's situation, the normal regimen of cefepime would be 2,000 mg (D_{norm}) every 12 hr (τ_{norm}). If one wanted to maintain D_{norm} at 2,000 mg, the extended dosing interval, τ_R, would be calculated as:

$$t_R = t_{norm} / Q$$

$$t_R = 12\ hr / 0.51$$

$$t_R \approx 24\ hr$$

It is important to monitor these patients on a continual basis as dose adjustments will be required if renal function significantly improves or worsens, if there are prolonged interruptions in the delivery of the CRRT therapy, or if CRRT is discontinued.

CONCLUSION

Patients with AKI or CKD and those receiving intermittent HD or CRRT present many challenges to the clinician as they are at increased risk for adverse events due to accumulation of drugs and/or their active or toxic metabolites. Important therapeutic decisions can be made based on awareness of each patient's functional renal capacity and of the effects of renal disease on drug metabolism, metabolite formation, and renal excretion. Clinicians can play a critical role in providing rational drug therapy to these patients making dose adjustments based on renal function using either traditional TDM or empiric methods, ensuring avoidance of drugs with toxic metabolites, determining the optimal dose to accommodate immediate post dialysis dosing, and taking responsibility for patient outcomes.

REFERENCES

1. United States Renal Data System. 2013 Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States. Bethesda, MD: National Institutes of Health, National Institutes of Diabetes and Digestive and Kidney Diseases; 2013.
2. Hoerger TJ, Simpson SA, Yarnoff BO, et al. The future burden of CKD in the United States: A simulation model for the CDC CKD initiative. *Am J Kidney Dis.* 2015;65(3):403-411.
3. Brochard L, Abroug F, Brenner M, et al. An official ATS/ERS/ESICM/SCCM/SRLF statement: prevention and management of acute renal failure in the ICU patient. *Am J Respir Crit Care Med.* 2010;181:1128-55.
4. Stevens LA, Coresh J, Greene T, et al. Comparative performance of the CKD epidemiology collaboration (CKD-EPI) and the modification of diet in renal disease (MDRD) study equations for estimating GFR levels above 60 mL/min/1.73 m^2. *Am J Kidney Dis.* 2010;56(3):486-95.
5. Spruill WJ, Wade WE, Cobb HH. Continuing the use of the Cockcroft-Gault equation for drug dosing in patients with impaired renal function. *Clin Pharmacol Ther.* 2009 Nov;86(5):468-70.
6. Gill J, Malyuk R, Djurdjev O, et al. Use of GFR equations to adjust drug doses in an elderly multi-ethnic group—a cautionary tale. *Nephrol Dial Transplant.* 2007;22(10):2894-9.
7. Melloni C, Peterson ED, Chen AY, et al. Cockcroft-Gault versus modification of diet in renal disease: importance of glomerular filtration rate formula for classification of chronic kidney disease in patients with non-ST-segment elevation acute coronary syndromes. *J Am Coll Cardiol.* 2008;51(10):991-6.
8. Dowling TC, Wang ES, Ferrucci L, et al. Glomerular filtration rate equations overestimate creatinine clearance in older individuals enrolled in the Baltimore Longitudinal Study on Aging: impact on renal drug dosing. *Pharmacotherapy.* 2013;33(9):912-21.
9. Park EJ, Wu K, Mi Z, et al. A systematic comparison of Cockcroft-Gault and MDRD equations for classification of kidney dysfunction and dosage adjustment. *Ann Pharmacother.* 2012;46(9):1174-87.
10. Bouchard J, Macedo E, Soroko S, et al. Comparison of methods for estimating glomerular filtration rate in critically ill patients with acute kidney injury. *Nephrol Dial Transplant.* 2010;25:102-7.
11. Dager W, Halilovic J. Acute kidney injury. In: Dipiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach, 9th ed.* New York: McGraw Hill; 2014.
12. Lee W, Kim RB. Transporters and renal drug elimination. *Ann Rev Pharmacol Toxicol.* 2004;44:137-66.
13. Masereeuw R, Russel FGM. Therapeutic implications of renal anionic drug transporters. *Pharmacol Ther.* 2010;126:200-16.
14. Moss DM, Neary M, Owen A. The role of drug transporters in the kidney: lessons from tenofovir. *Front Pharmacol.* 2014;5:248.
15. Westenfelder C, Arevalo G, Crawford P, et al. Renal tubular function in glycerol-induced acute renal failure. *Kidney Int.* 1980;18:432-44.
16. Bricker NS, Klahr S, Lubowitz H, et al. The pathophysiology of renal insufficiency. On the functional transformations in the residual nephrons with advancing disease. *Ped Clin N Am.* 1971;18(2):595-611.
17. Tozer TN. Nomogram for modification of dosage regimens in patients with chronic renal impairment. *J Pharmacokinet Biopharm.* 1974;2:13-28.
18. Dowling TC, Frye RF, Fraley DS, et al. Comparison of iothalamate clearance methods for measuring GFR. *Pharmacother.* 1999;19(8):943-50.
19. Liu S, Beringer PM, Hidayat L, et al. Probenecid, but not cystic fibrosis, alters the total and renal clearance of fexofenadine. *J Clin Pharmacol.* 2008 Aug;48(8):957-65.
20. Wang ZJ, Yin OQ, Tomlinson B, et al. OCT2 polymorphisms and in-vivo renal functional consequence: studies with metformin and cimetidine. *Pharmacogenet Genomics.* 2008;18(7):637-45.

21. Shu Y, Brown C, Castro RA, et al. Effect of genetic variation in the organic cation transporter 1, OCT1, on metformin pharmacokinetics. *Clin Pharmacol Ther.* 2008;83(2):273-80.
22. Landersdorfer CB, Kirkpatrick CM, Kinzig M, et al. Competitive inhibition of renal tubular secretion of ciprofloxacin and metabolite by probenecid. *Br J Clin Pharmacol.* 2010;69(2):167-78.
23. Mirapex® [package insert]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; 2015.
24. Dreisbach AW. The influence of chronic renal failure on drug metabolism and transport. *Clin Pharmacol Ther.* 2009;86:553-6.
25. Vilay AM, Churchwell MD, Mueller BA. Drug metabolism and clearance in acute kidney injury. *Crit Care.* 2008;12:235.
26. Flockhart DA. Cytochrome P450 Drug Interaction Table. http://medicine.iupui.edu/clinpharm/ddis/table.asp. Accessed October 18, 2015.
27. Nolin TD. Altered nonrenal drug clearance in ESRD. *Curr Opin Nephrol Hypertens.* 2008;17(6):555-9.
28. Mouton JW, Touzw DJ, Horrevorts AM, et al. Comparative pharmacokinetics of the carbapenems: clinical implications. *Clin Pharmacokinet.* 2000;39(3):185-201.
29. Guevin C, Michaud J, Naud J, et al. Down-regulation of hepatic cytochrome p450 in chronic renal failure: role of uremic mediators. *Br J Pharmacol.* 2002;137(7):1039-46.
30. Dowling TC, Briglia AE, Fink JC, et al. Characterization of hepatic cytochrome p4503A activity in patients with end-stage renal disease. *Clin Pharmacol Ther*. 2003;73:427-34.
31. Fleishaker JC. Clinical pharmacokinetics of reboxetine, a selective norepinephrine reuptake inhibitor for the treatment of patients with depression. *Clin Pharmacokinet*. 2000;39:413-27.
32. Cerqueira PM, Coelho EB, Geleilete TJ, et al. Influence of chronic renal failure on stereoselective metoprolol metabolism in hypertensive patients. *J Clin Pharmacol.* 2005;45:1422-33.
33. Aronson JK. Clinical pharmacokinetics of digoxin 1980. *Clin Pharmacokinet*. 1980;5:137-49.
34. Fish DN. Fluoroquinolone adverse effects and drug interactions. *Pharmacotherapy*. 2001;21(10: Part 2):253S-72S.
35. Greig SL, Plosker GL. Sucroferric oxyhydride: a review in hyperphosphataemia in chronic kidney disease patients undergoing dialysis. *Drugs* 2015;75(5):533-42.
36. Mohammad RA, Matzke GR. Drug therapy individualization for patients with chronic kidney disease. In: Dipiro JT, Talbert RL, Yee GC, et al., eds. *Pharmacotherapy: A Pathophysiologic Approach, 9th ed.* New York: McGraw Hill; 2014.
37. Gilbert B, Robbins P, Livornese LL Jr. Use of antibacterial agents in renal failure. *Infect Dis Clin North Am.* 2009;23:899-924.
38. Olyaei, AJ, Bennett WM. Drug dosing in the elderly patients with chronic kidney disease. *Clin Geriatr Med.* 2009;25:459-527.
39. Grandison MK, Boudinot FD. Age-related changes in protein binding of drugs: implications for therapy. *Clin Pharmacokinet.* 2000;38:271-90.
40. Meijers BKI, Bammens B, Verbeke B, et al. A review of albumin binding in CKD. *Am J Kidney Dis.* 2008;51:839-50.
41. Chan GL, Axelson JE, Price JD, et al. In vitro protein binding of propafenone in normal and uraemic human sera. *Eur J Clin Pharmacol.* 1989;36:495-9.
42. Pritchard JF, Matzke GR, Opsahl JA, et al. Effects of hemodialysis on plasma protein binding of bepridil. *J Clin Pharmacol.* 1995;35:137-41.
43. Dowling TC, Murphy JE, Matzke GR, et al. Evaluation of renal drug dosing: prescribing information and clinical pharmacist approaches. *Pharmacotherapy.* 2010;30:776-86.
44. Dettli L. Elimination kinetics and dosage adjustments of drugs in patients with kidney disease. *Prog Pharmacol.* 1977;1:1-34.
45. Pai AB, Cardone KE, Manley HJ, et al. Medication reconciliation and therapy management in dialysis-dependent patients: need for a systematic approach. *Clin J Am Soc Nephrol.* 2013;8:1988-99.
46. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. *Eur J Clin Pharmacol.* 2009;65:757-73.
47. McEvoy GK, Snow EK. *American Hospital Formulary Service Drug Information.* Bethesda, MD: American Society of Health-System Pharmacists; 2015.
48. Aronoff GR, Bennett WM, Berns JS, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults and Children.* 5th ed. Philadelphia: American College of Physicians; 2007.
49. Thummel KE, Shen DD, Isoherranen N. Appendix II. Design and optimization of dosage regimens: Pharmacokinetic data. In: Brunton LL, Lazo JS, Parker KL, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 12th ed. New York: McGraw-Hill; 2011.
50. Joy MS, DeHart RM, Gilmartin C, et al. Clinical pharmacists as multidisciplinary health care providers in the management of CKD: A joint opinion by the Nephrology and Ambulatory Care Practice and Research Networks of the American College of Clinical Pharmacy. *Am J Kidney Dis.* 2005;45:1105-18.
51. Secker, BS, Mueller BA, Sowinski KM. Drug dosing considerations in alternative hemodialysis. *Adv Chr Kidney Dis.* 2007;14:e17-e26.
52. Dager WE, King JH. Aminoglycosides in intermittent hemodialysis: pharmacokinetics with individual dosing. *Ann Pharmacother.* 2006;40:9-14.

53. Matzke GR. Status of hemodialysis of drugs in 2002. *J Pharm Pract.* 2002;15:405-18.
54. Schulman G. Clinical application of high-efficiency hemodialysis. In: Nissenson AR, Fine RN, eds. *Handbook of Dialysis Therapy.* 4th ed. Philadelphia: Saunders/Elsevier; 2008:481-97.
55. Agarwal R, Mehrotra R. End-Stage renal disease and dialysis. *NephSAP.* 2010;9:352-414.
56. Wong J, Vilar E, Davenport A, et al. Incremental hemodialysis. *Nephrol Dial Transplant* 2015;30:1639-48.
57. Heintz BH, Matzke GR, Dager WE. Antimicrobial dosing concepts and recommendation for critically ill patients receiving continuous renal replacement therapy or intermittent hemodialysis. *Pharmacotherapy.* 2009;29:562-77.
58. Mueller BA, Pasko DA, Sowinski KM. Higher renal replacement therapy dose delivery influences on drug therapy. *Artif Organs.* 2003;27:808-14.
59. Scott MK, Macias WL, Kraus MA, et al. Effects of dialysis membrane on intradialytic vancomycin administration. *Pharmacotherapy.* 1997;17:256-62.
60. Mohamed OHK, Wahba IM, Watnick S, et al. Administration of tobramycin in the beginning of the hemodialysis session: A novel intradialytic dosing regimen. *Clin J Am Soc Nephrol.* 2007;2:694-9.
61. Churchwell MD, Mueller BA. Drug dosing during continuous renal replacement therapy. *Semin Dial.* 2009;22:185-8.
62. Eyler RF, Mueller BA. Antibiotic dosing in critically ill patients with acute kidney injury. *Nat Rev Nephrol* 2011;7(4):226-35.
63. Matzke GR, Dowling TC, Marks SA, et al. Influence of kidney disease on drug disposition: An assessment of industry studies submitted to FDA for new chemical entities 1999-2010. *J Clin Pharmacol.* 2015 (Aug 4). doi: 10.1002/jcph.604. [Epub ahead of print].
64. Matzke GR, Aronoff GR, Atkinson AJ, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2011;80:1122-37.
65. Fissell WH. Antimicrobial dosing in acute renal replacement. *Adv Chronic Kidney Dis*. 2013;20(1):85-93.
66. Karyekar CS, Eddington ND, Briglia A, et al. Renal interaction between itraconazole and cimetidine. *J Clin Pharmacol*. 2004;44:919-27.