Chapter 67: Personalized Pharmacotherapy for Patients with Chronic Kidney Disease

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KEY CONCEPTS

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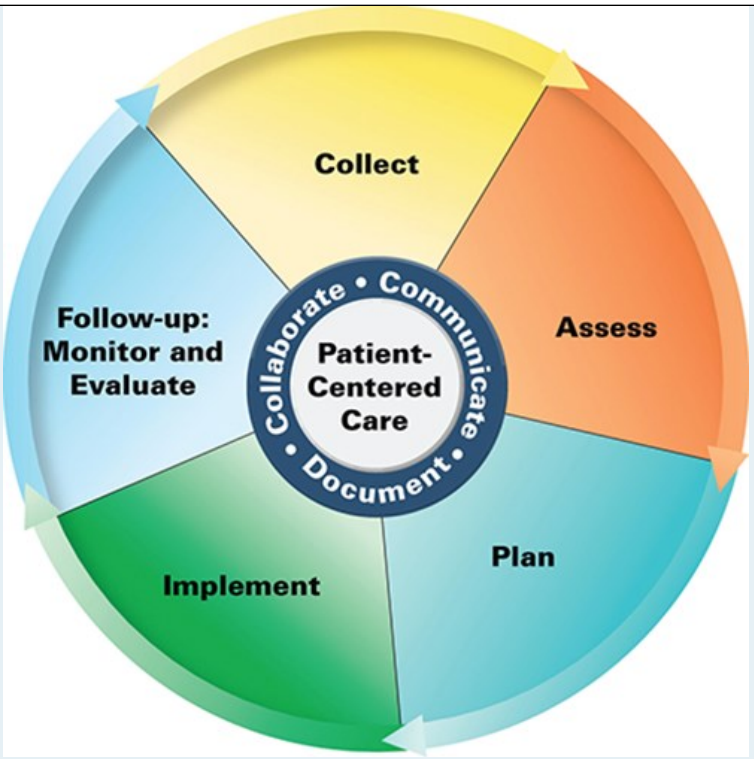
1. Chronic kidney disease (CKD) and related comorbidities can impact processes contributing to medication absorption and bioavailability, but the significance of these changes is ill-defined for most medications.
2. The volume of distribution (V_D) of many medications is increased in the presence of acute kidney injury (AKI) and CKD secondary to volume expansion and/or decreased protein binding.
3. Renal clearance (CL_R) is a composite of renal excretory functions (filtration, secretion, and reabsorption. These functions decline in the setting of CKD, causing accumulation of medications that are predominantly renally excreted.
4. Nonrenal clearance (CL_{NR}) may be altered in CKD, causing accumulation of medications that are predominantly cleared by metabolism and/or transport.
5. Although information on pharmacokinetics and medication dosing in patients with CKD has improved in recent years, dosing guidelines remain highly variable and many are not optimal for clinical use.
6. Individualization of a medication dosage regimen for a patient with CKD is based on the pharmacodynamic/pharmacokinetic characteristics of the medication, the patient's degree of residual kidney function, and the patient's overall clinical condition.
7. The effect of dialysis on medication elimination is dependent on the characteristics of the medication and the dialysis prescription. Hemodialysis (HD) clearance data can be used to guide the initial medication dosage regimen recommendation; however, prospective monitoring of serum concentrations is often warranted, especially for narrow therapeutic index drugs.

PATIENT CARE PROCESS

Patient Care Process for Personalizing Pharmacotherapy in Patients with Chronic Kidney Disease



Collect

- Patient characteristics (e.g., age, sex, height, weight)
- Patient medical history (personal and family)
- Social history (e.g., use of tobacco, alcohol, other substances of misuse)
- Current medications including over-the-counter products, and herbal/dietary supplements
- Objective data
  - Labs, including serum creatinine and/or cystatin C

Assess

- Kidney function
  - Estimated GFR or CL_{Cr} for medication dosing, based on best available methodology (see Chapter e60)
  - Measured CL_{Cr} or GFR as confirmatory test if needed
- Medication regimen
  - Indication and treatment goals for all medications
  - Potential drug-drug interactions
  - Identify medications requiring adjustment to the dosage regimen (see Table 67-3)

Plan*

- Adjusted dosage regimen as needed for each medication
  - Calculate adjusted regimen (dose and frequency) based on pharmacokinetic characteristics and patient's kidney function (see Tables 67-4 and 67-5)
- Treatment goals and corresponding monitoring parameters

Implement*

- Provide patient education regarding all elements of treatment plan
- Discontinue or avoid prescription of nephrotoxic medication if possible

Follow-up: Monitor and Evaluate

- Medication serum concentrations if therapeutic drug monitoring is available/applicable
- Parameters of medication response and toxicity
- Kidney function (every 3 to 5 days for acute therapies, monthly or quarterly for chronic therapies)
- Revise regimen based on medication response or change in patient status (including change in kidney function)
- Patient adherence to treatment plan

* ***Collaborate with patient, caregivers, and other health professionals.***

BEYOND THE BOOK

BEYOND THE BOOK

Visit the US National Library of Medicine website DailyMed (https://dailymed.nlm.nih.gov/dailymed/index.cfm), which is the official provider of US Food and Drug Administration (FDA)-approved medication label information (i.e., package inserts). Identify two medications that require renal dose adjustment in CKD, including, one that is predominantly renally excreted ($f_e > 0.3$) and one that is not ($f_e < 0.3$). Review the renal dosing adjustment recommendations, and develop a table that compares and contrasts the kidney function cutoffs for dose adjustment, the kidney function estimate (i.e., creatinine clearance, glomerular filtration rate) upon which the recommendations are based, and the dosage regimen adjustment strategy used (i.e., decrease dose or increase dosing interval). This activity is useful to enhance student understanding of the ASSESS and PLAN steps in the patient care process.

INTRODUCTION

Chronic kidney disease (CKD) is defined by the presence of abnormalities of kidney function or structure for more than 3 months (see Chapter e60, "Evaluation of Kidney Function" and Chapter 62, "Chronic Kidney Disease").[1] The Kidney Disease: Improving Global Outcomes (KDIGO) CKD categories by GFR cutoff are depicted in Fig. 62-1. About 10% to 15% of the global population and 1 in 7 US adults have CKD.[2-5] CKD patients are characterized by a high prevalence of polypharmacy, with a median of eight prescribed medications per patient and up to 90% of CKD patients taking over five medications daily.[6,7] Therefore, understanding the changes in pharmacokinetics, pharmacodynamics, and medication dosing in this patient population is crucial for personalizing pharmacotherapy and optimizing pharmacotherapeutic outcomes.

CKD patients exhibit altered pharmacokinetics and/or pharmacodynamics due to disease-related physiologic and biochemical changes, including altered renal excretory function, protein binding, and cytochrome P450 enzyme and/or transporter activity.[8-15] Changes to medication absorption and

bioavailability are not well quantified, while changes to distribution and elimination are better described. Medications with a high fraction excreted unchanged in the urine ($f_e > 0.3$) may accumulate in CKD patients due to a decline in the renal excretory functions (filtration, secretion, and reabsorption) that compose renal clearance (CL_R). Medications that are not predominantly renally eliminated (i.e., are predominantly eliminated by metabolism and/or transport) may also accumulate in patients with CKD secondary to changes in nonrenal clearance (CL_{NR}).

In CKD patients, the dosage regimens of numerous medications must be altered to prevent toxicity without compromising the desired therapeutic benefit.[11,16] An accurate assessment of patient kidney function is a crucial first step in renal dose adjustment. Despite conduction of more renal impairment studies by industry and improvements in product labeling language, challenges remain for determining medication dose adjustments in CKD patients.[17] If there is no official dosage regimen recommendation in the product labeling, an adjustment may be calculated on the basis of the medication's f_e and the patient's residual kidney function.[18] For medications that are extensively metabolized or for which dramatic changes in protein binding and/or volume of distribution (V_D) have been noted, a complex adjustment strategy may need to be employed.[19,20] For patients receiving chronic renal replacement therapy (i.e., dialysis), medication dosage adjustments will be based on characteristics of the drug, the dialysis prescription, and the clinical setting for which dialysis is being performed, and prospective monitoring of serum drug concentrations may be warranted.[19]

Clinicians will often need to design individualized therapeutic regimens to optimize clinical outcomes in patients with CKD.[11] In this chapter, the influence of CKD on pharmacokinetics and pharmacodynamics is examined. A general approach to personalizing pharmacotherapy, with emphasis on medication selection and dosing strategies for CKD patients, is presented. Finally, the impact of chronic renal replacement therapy on drug disposition is discussed. Medication dosage adjustment strategies for patients with acute kidney injury (AKI), including those who are receiving continuous renal replacement therapy, are presented in Chapter 61, "Acute Kidney Injury."

PHARMACOKINETIC AND PHARMACODYNAMIC CHANGES IN CHRONIC KIDNEY DISEASE

The pharmacokinetics and pharmacodynamics of numerous medications are altered by CKD.[8-14] An understanding of why and how pharmacokinetic processes are impacted by CKD provides a framework to project the influence of CKD on emerging therapies. In addition, these effects can be factored into the clinician's dosage recommendations for individual CKD patients.

Absorption and Bioavailability

1 Bioavailability describes the fraction of medication reaching systemic circulation following extravascular administration. Oral bioavailability is dependent on absorption from the gastrointestinal (GI) tract and pre-systemic (i.e., intestinal and hepatic) metabolism and transport. There is relatively little quantitative information regarding the influence of CKD on medication absorption and bioavailability. Most evaluations of medication absorption in CKD assess changes to peak medication serum concentration (C_{max}) and the time at which the peak serum concentration is achieved (t_{max}) rather than oral bioavailability (i.e., a comparison of the area under the concentration-time curve [*AUC*] after oral and intravenous [IV] administration). Changes to absorption processes are likely the result of complex interplay between disease-related physiologic changes and drug-drug interactions.[8-15,21]

Altered absorption and/or bioavailability of medications in CKD patients may be a consequence of changes to GI physiologic and biochemical processes secondary to CKD and related comorbidities. These changes include decreased gastric mobility, decreased gastric acidity, GI edema, and altered pre-systemic metabolism and/or transport.[8-15,21] Decreased GI motility can occur in CKD patients secondary to diabetic gastroparesis and may delay t_{max} and decrease C_{max}, thereby altering a medication's absorption profile without impacting its bioavailability. Gastric acidity may decrease (i.e., an increase in gastric pH) in CKD patients due to urea retention and subsequent conversion to ammonia by gastric urease. This alkalization may alter the dissolution or ionization properties of weakly basic drugs and lead to changes in absorption. Edema of the GI tract secondary to concomitant cirrhosis or congestive heart failure can also decrease the absorption of some medications, such as furosemide. Finally, the bioavailability of some medications (e.g., dihydrocodeine, felodipine, sertraline, and cyclosporine) may be increased in CKD patients due to alterations in pre-systemic (i.e., intestinal and hepatic) metabolism and/or transport that increases the amount of parent drug reaching systemic circulation (i.e., decreased metabolism, increased uptake, and/or decreased efflux, see Nonrenal Clearance below).

Drug interactions can also alter the absorption and/or bioavailability of other medications through a variety of mechanisms.[8] Although not disease-specific effects, these drug-drug interactions are worth noting due to the high medication burden of CKD patients.[6,7] Administration of antacids, H_2-receptor antagonists, proton pump inhibitors, and phosphate binders can decrease gastric acidity and lower the bioavailability of several medications, such as some antibiotics and digoxin. Antacids and vitamin supplements can form insoluble salts or metal ion chelates with some medications and decrease their bioavailability. Finally, drug interactions that modulate pre-systemic intestinal and hepatic metabolism and/or transport may alter bioavailability.

Distribution

A medication's volume of distribution (V_D) reflects the extent of distribution throughout the body.[8,10] Lower V_D values reflect distribution primarily in the vascular space, whereas higher V_D values reflect extensive distribution outside the vascular space (i.e., in the tissues). The V_D of numerous medications is increased in CKD and AKI patients as a result of fluid overload, altered protein binding, and/or altered tissue binding, leading to a decrease in serum drug concentrations. The V_D of a few medications may be decreased in the setting of CKD, likely due to decreased tissue binding (Table 67-1).[8,10,12-14]

TABLE 67-1

Volume of Distribution of Selected Medications in Patients with ESKD

Medication	Normal (L/kg)	ESKD (L/kg)	Change from Normal
Increased			
Amikacin	0.20	0.29	45%
Cefazolin	0.13	0.17	31%
Cefoxitin	0.16	0.26	63%
Ceftriaxone	0.28	0.48	71%
Cefuroxime	0.20	0.26	30%
Doripenem	0.25	0.47	88%
Dicloxacillin	0.08	0.18	125%
Erythromycin	0.57	1.09	91%
Furosemide	0.11	0.18	64%
Gentamicin	0.20	0.32	60%
Isoniazid	0.60	0.80	33%
Minoxidil	2.60	4.90	88%
Naproxen	0.12	0.17	42%
Phenytoin	0.64	1.40	119%

Trimethoprim	1.36	1.83	35%
Vancomycin	0.64	0.85	33%
Decreased			
Atenolol	1.20	0.90	-25%
Chloramphenicol	0.87	0.60	-31%
Ciprofloxacin	2.50	1.95	-22%
Digoxin	7.30	4.00	-45%
Ethambutol	3.70	1.60	-57%
Methicillin	0.45	0.30	-33%
Metoprolol	5.60	1.00	-82%
Pindolol	2.10	1.10	-48%
Propranolol	4.40	3.60	-18%

ESKD, end-stage kidney disease.

Data from References 12 to 14.

Fluid Status

Variability in fluid status is a common issue in patients with AKI and severe CKD (category G4 and G5), especially those who are critically ill. Many critically ill patients receive large volumes of IV fluids for resuscitation from shock, and can subsequently develop edema, pleural effusions, or ascites. Furthermore, AKI and CKD can precipitate decreased water excretion. These factors can lead to fluid overload and, subsequently, an increase in V_D and a decrease in serum concentrations. This is especially problematic with hydrophilic medications, such as aminoglycosides and cephalosporins.[8,10,11]

Altered Plasma Protein Binding

Protein binding limits medication distribution, as only unbound or “free” medication can cross cellular membranes and distribute outside the vascular space. Albumin is a major drug-binding plasma protein that primarily binds acidic medications and exhibits decreased plasma concentrations in CKD.[8] Protein binding of many acidic medications, such as penicillins, cephalosporins, aminoglycosides, furosemide, and phenytoin, is therefore decreased in the setting of CKD secondary to hypoalbuminemia, qualitative changes in the conformation of the albumin binding site, and/or competition for binding sites by other medications, metabolites, and endogenous substances.[8,12,13,15] This increases the apparent V_D. Ultimately, a new equilibrium is established as a result of increased medication elimination/distribution, such that the unbound concentrations remain comparable to those observed in patients with normal kidney function despite the fact that total concentrations are decreased. Thus, the net effect is an alteration in the relationship between total medication concentration and pharmacodynamic effect.

For example, protein binding of phenytoin (90% protein-bound, primarily to albumin) is dramatically decreased in CKD secondary to hypoalbuminemia and decreased plasma phenytoin binding affinity for albumin. These changes alter the relationship between total phenytoin concentration and therapeutic and toxic effects.[22] The increase in unbound fraction, from values of 10% in those with normal kidney function to 20%

or more in those with G5 CKD, results in increased hepatic clearance and decreased total concentrations. Thus, in patients with CKD, the therapeutic range based on total phenytoin concentration is shifted downward from normal values of 10 to 20 mg/L (μg/mL; 40-79 μmol/L) to values as low as 4 to 8 mg/L (μg/mL; 16-32 μmol/L). Since the unbound concentration therapeutic range is the same for all patients, 1 to 2 mg/L (μg/mL; 4-8 μmol/L), this measurement provides the best target for individualizing phenytoin therapy in patients with CKD.

One can approximate the total phenytoin concentration that would be observed in category G5 CKD patients assuming they had normal plasma protein binding ($C_{\text{normal binding}}$). The estimated total phenytoin concentration can then be interpreted in light of the usual total therapeutic range to assess the patient's response to therapy.[22] For normal or low albumin (concentration expressed in g/dL; albumin expressed in g/L must be multiplied by 0.1 prior to using the following equation) and category G5 CKD:

$$C_{\text{normal binding}} = C_{\text{reported}}/[(0.9)(0.48)(\text{albumin}/4.40)] + 0.1$$

where $C_{\text{normal binding}}$ = total phenytoin concentration that would be observed assuming patient had normal protein binding, and C_{reported} = patient's total phenytoin concentration reported by the laboratory (represents decreased plasma protein binding).

α1-acid glycoprotein is another major drug-binding plasma protein which primarily binds basic medications and exhibits increased plasma concentrations in CKD. For most medications that bind to α1-acid glycoprotein, protein binding is unaffected by CKD. However, for some medications (e.g., bepridil, disopyramide), the unbound fraction may be dramatically decreased and the V_D decreased in CKD patients, especially kidney transplant and HD patients.[8,13,19]

Altered Tissue Binding

Distribution may also be affected by altered tissue binding of medications in CKD patients; this is relatively rare and limited to few medications, such as pindolol, ethambutol, and, most notably, digoxin.[13] The V_D of digoxin is decreased by up to 50% in patients with category G5 CKD, leading to elevated serum concentrations.[23] In this case, the absolute amount of digoxin bound to the receptor is decreased and the resultant serum digoxin concentration is higher than anticipated. Thus, in CKD patients, particularly in those with category G5, a "normal" total medication concentration may be associated with either an adverse reaction secondary to elevated unbound medication concentrations, or a subtherapeutic response because of an altered plasma-to-tissue medication concentration ratio. The monitoring of unbound medication concentrations in CKD patients is thus warranted for those medications that have a narrow therapeutic range, are highly protein bound (unbound fraction of less than 20%), and for which marked variability in the unbound fraction is possible (e.g., phenytoin and disopyramide).

V_D Calculation Method

Finally, determination of the influence of CKD on V_D may depend on the method used to calculate V_D. The three most commonly used volume of distribution terms are: volume of the central compartment (V_C, which relates drug concentration and amount immediately following IV bolus administration), volume of the terminal phase (V_β and V_{area}, which relates drug concentration and amount during the terminal elimination phase), and volume of distribution at steady state (V_{ss}, which relates drug concentration and amount at IV infusion steady state). For many medications, V_c approximates extracellular fluid volume and thus may be increased or decreased by acute changes in fluid status; oliguric AKI is often accompanied by fluid overload and a resultant increased V_c for many medications. V_{area} and V_β are affected by both distribution and the terminal elimination rate constant, whereas V_{ss} has the advantage of being independent of medication elimination. Therefore, V_{ss} is the most appropriate volume term to use when one desires to compare drug distribution volumes between patients with CKD and those with normal kidney function.[24]

Elimination

Elimination of medication from the body is characterized in pharmacokinetic terms as total systemic clearance (CL_T). CL_T is the sum of all organ clearances and can be defined simply as the sum of renal clearance (CL_R) and nonrenal clearance (CL_{NR}).[8,10,13] Both CL_R and CL_{NR} can be altered in the setting of CKD.

Renal Clearance

3 Kidney function is the most quantifiable determinant of medication clearance. CL_R is a composite of all renal excretory functions, namely, filtration, tubular secretion, and tubular reabsorption ($CL_R = CL_{filtration} + CL_{secretion} - CL_{reabsorption}$).[10,12,13] Filtration clearance occurs by diffusion and is a function of GFR and the fraction of the medication that is unbound to plasma proteins (f_u) and thus available to be freely filtered ($CL_{filtration} = GFR \times f_u$). Tubular secretion and reabsorption are bidirectional processes that involve carrier-mediated renal transport systems consisting of uptake and efflux transporters located on the basolateral and apical membranes of tubular cells, respectively.[13,25,26]

Renal transport systems have been broadly classified on the basis of substrate selectivity into the anionic and cationic renal transport systems, which are responsible for the transport of a number of organic acidic and basic medications, respectively.[13,25,26] Basolateral uptake of medications into renal tubular cells from the plasma is mediated primarily by organic anion transporters (OATs), organic anion transporting polypeptides (OATPs), and organic cation transporters (OCTs). Apical efflux of medications from renal tubular cells to the tubular lumen is mediated primarily by multidrug resistance proteins (MRPs), breast cancer resistance protein (BCRP), P-glycoprotein (P-gp), multidrug and toxin extrusion proteins (MATEs), and organic cation/carnitine transporters (OCTNs). Many drugs are actively secreted by one or more of these transporter families.[25]

Medications that are majority excreted via the renal route (i.e., $f_e > 0.3$) are likely to have their pharmacokinetics altered by decreases in CL_R secondary to CKD.[17] Reduction in kidney mass, the number of functioning nephrons, renal blood flow, GFR, and/or the rate of tubular secretion and reabsorption all contribute to the decreased renal excretory capacity observed in CKD.[8] The intact nephron hypothesis describes the anatomic and physiologic changes to the nephron population in CKD and states that as CKD progresses, all facets of renal excretory function (filtration, secretion, and reabsorption) will decline in parallel.[27,28] However, CL_R of medications may violate the intact nephron hypothesis in that renal secretory function may decline more quickly or more slowly than renal filtration function.[29-31] For example, OAT1 and OAT3 substrates exhibit a greater decline in $CL_{secretion}$ than $CL_{filtration}$ in patients with severe CKD, suggesting that tubular secretion declines more quickly than glomerular filtration.[29,31] The impact of CKD on renal secretory function is dependent on the transporter systems involved in clearance and/or the medication being secreted.[30]

For medications that are primarily filtered, a decrease in GFR will result in a proportional decrease in CL_R. However, for medications that are highly secreted, a decrease in GFR may result in a variable decrease in CL_R depending on the relative decline in secretory function compared to GFR. Therefore, the impact of CKD on CL_R of a medication may depend on the renal excretory profile of the drug (i.e., the relative contributions of filtration, secretion, and reabsorption to overall CL_R, and the relevant transporter pathways involved in secretion and reabsorption).[30]

Nonrenal Clearance

4 CL_{NR} encompasses all routes of medication elimination other than renal excretion of unchanged drug, and broadly includes hepatic and extrahepatic metabolism and transcellular transport pathways. Major CL_{NR} pathways include oxidative metabolism by cytochrome P450s (CYPs), conjugative metabolism by uridine diphosphate-glucuronosyltransferases (UGTs), and transport by OATPs, MRPs, BCRP, and other transporters.[9,10,15,32] CKD, and particularly end-stage kidney disease (ESKD), impacts CL_{NR} of many drugs (Table 67-2), and over 30% of medications with $f_e < 0.3$ require a renal dose adjustment.[13,14,17,33] The impact of CKD on CL_{NR} is due largely to altered activity of drug-metabolizing enzymes and transporters in the liver and other organs. It is believed that these effects are due to accumulation of solutes that would otherwise be renally cleared in CKD patients (i.e., uremic solutes), which may inhibit drug-metabolizing enzymes and/or transporters by downregulation of mRNA and/or protein expression and/or by direct inhibition.[8,10,13-15]

TABLE 67-2

Impact of ESKD on CL_{NR} of Selected Medications

Medication	Decrease in CL_{NR}

Acyclovir	50%
Aztreonam	33%
Bupropion	↓
Captopril	50%
Carvedilol	↓
Cefotaxime	40%
Ceftriaxone	↓
Cimetidine	46%
Ciprofloxacin	33%
Doripenem	↓
Erythromycin	↓
Imipenem	58%
Isoniazid	↓
Ketorolac	↓
Losartan	↓
Lovastatin	↓
Metoclopramide	66%
Minoxidil	46%
Morphine	40%
Nicardipine	37%
Nimodipine	87%
Nortriptyline	↓
Procainamide	60%
Quinapril	↓
Raloxifene	↓
Repaglinide	↓

Rosuvastatin	↓
Simvastatin	↓
Valsartan	↓
Vancomycin	43%
Verapamil	54%
Warfarin	50%

CL_{NR}, nonrenal clearance; ESKD, end-stage kidney disease.

↓ a decrease is documented but not quantified.

Data from References 13, 14, and 33.

Importantly, the impact of CKD on CL_{NR} is pathway-specific; not all metabolizing enzymes and transporters are impacted by CKD or altered to the same magnitude by CKD. Generally, Drug metabolizing enzymes are only modestly affected by CKD. For example, the activities of CYP1A2, CYP2C8, CYP2C9, and CYP2C19 do not appear to be altered to a clinically significant extent in CKD. Conversely, the activity of CYP2D6 may be decreased in CKD.[34-36] The activity of CYP3A4 in CKD is of great interest, considering CYP3A4 is responsible for the metabolism of many medications on the market. Although there are conflicting clinical reports, it has been shown that CYP3A4 activity is generally preserved in patients with CKD.[8,10,13-15,36-38] Conversely, the activity of extrarenal transporters may often be affected by CKD. For example, there is a 40% to 60% decrease in hepatic OATP activity in patients with severe CKD.[34,35] Furthermore, the effect of CKD on CL_{NR} may depend partly on whether the decrease in kidney function is acute or chronic. For example, higher residual CL_{NR} has been documented in AKI versus CKD for patients with comparable creatinine clearance (CL_{cr}). receiving vancomycin and imipenem.[11,15,39,40]

CKD-associated changes to CL_{NR} are complex and the result of pathway-specific changes to CL_{NR} and overlapping substrate specificity of medication for multiple drug-metabolizing enzymes and/or transporters. Therefore, prediction of the effect of kidney disease on the metabolism of a particular medication is difficult and there is no quantitative strategy to predict changes for one medication based on data from another, even if they are in the same pharmacologic class. However, some qualitative insight can be gained if one knows what enzyme or transporter is involved in the elimination of the drug of interest and how the enzyme or transporter is affected by CKD.

Accumulation of Metabolites

CKD patients who are receiving chronic pharmacotherapy may experience considerable accumulation of metabolite(s) as well as the parent compound, particularly if the ultimate route of metabolite elimination is renal. Metabolites of several medications have significant pharmacologic and/or toxicologic activity. However, the pharmacokinetics and pharmacodynamics of metabolites are not often fully elucidated during the drug development process. Because of the multiplicity of potential interactions of compounds that are primarily metabolized, the practical consequences of metabolite accumulation are difficult to predict and are most often identified in patients at risk serendipitously.

The metabolite may have similar pharmacologic activity to the parent drug and thus contribute significantly to clinical and toxicologic response.[16] For example, the liver rapidly metabolizes morphine into active metabolites, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G), which readily cross the blood-brain barrier, bind to opiate receptors, and exert strong analgesic effects. In CKD patients, morphine is metabolized more slowly, and clearance of M3G and M6G decreases, resulting in prolonged narcosis and respiratory depression.[41] Alternatively, the metabolite may have qualitatively dissimilar pharmacologic action compared to the parent drug. For example, meperidine undergoes *N*-demethylation metabolism by various CYP450 isoforms to form normeperidine. Whereas meperidine has central nervous system depressant effects, normeperidine has stimulatory

activity that may produce seizures.[42]

Pharmacodynamics

CKD affects multiple organ systems, and therefore the response to a medication may change beyond what would be predicted based on pharmacokinetic changes alone. For example, enoxaparin dosage reduction is required in category G4 and G5 CKD patients.[43,44] This is due to the accumulation of uremic solutes which results in complex disturbances of the coagulation system leading to an increase in bleeding. Therefore, it seems that dosage adjustment solely based on kidney function may not always lead to optimal anticoagulation outcomes in CKD patients.

Successful antibiotic or antiviral treatment of CKD patients requires not only consideration of pharmacokinetic profiles, but also the medications' pharmacodynamics, which links measures of systemic exposure (such as peak and trough serum concentrations, and *AUC*) to bacteriologic activity.[10] Most antibiotics demonstrate concentration-dependent or time-dependent bacterial killing. For concentration-dependent antibiotics, such as fluoroquinolones or aminoglycosides, a high ratio of the peak serum concentration to the minimum inhibitory concentration (MIC, the minimum concentration required to inhibit bacterial growth) has been associated with increased likelihood of clinical success. Conversely, for time-dependent antibiotics, such as cephalosporins, the percentage of the dosing interval spent above the MIC is the most important pharmacodynamic parameter to maximize clinical success. This has led to the utilization of prolonged infusions or continuous infusions. Thus, it is necessary to administer anti-infective medications with a time-dependent action more frequently, whereas anti-infective medications with a concentration-dependent action should be administered with a higher maintenance dose and potentially a prolonged dosage interval to increase efficacy while minimizing toxicity. Therefore, both the pharmacodynamics and pharmacokinetics of medications may need to be considered when initiating antimicrobial therapy in CKD patients.

MEDICATION DOSAGE REGIMEN INDIVIDUALIZATION IN CHRONIC KIDNEY DISEASE

Determining the appropriate dose of medication for a patient with CKD is dependent on both patient- and medication-specific factors.[11,16] Obtaining a full clinical picture of the patient, including an accurate assessment of kidney function, is imperative. Furthermore, a thorough understanding of how CKD impacts the pharmacokinetics of the medication being prescribed, and, if available, corresponding dose adjustment recommendations, is necessary to individualize pharmacotherapy. The patient care process for personalizing pharmacotherapy in patients with CKD involves a stepwise approach for adjusting medication dosage.

Estimation of Kidney Function for Personalizing Pharmacotherapy

Accurate assessment of kidney function is a critical step in determining appropriate medication dosing regimens, and the KDIGO guidelines recommend utilizing the most accurate method to assess kidney function for an individual patient.[16] A detailed discussion of the methodologies for assessing kidney function is presented in Chapter e60, "Evaluation of Kidney Function." The most common equations for estimating GFR include the Cockcroft-Gault (CG) equation (which calculates estimated creatinine clearance [eCL_{cr}]) and the several iterations of the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equations (which calculate estimated GFR [eGFR]).[45-48] CG has been the most commonly used method to estimate kidney function for medication dosing for over 40 years; however, contemporary eGFR equations offer improved accuracy and precision over CG and are automatically reported in the clinical setting.[46,49]

There is considerable debate regarding which equation to estimate kidney function is the most appropriate to use for medication dosing. The CKD-EPI equations offer increased accuracy over CG.[46,47] However, for most medications, any renal pharmacokinetic studies were performed and dosing guidelines were developed using CG, and some argue that renal dose adjustment based on eGFR may be inappropriate.[50,51] Furthermore, the CKD-EPI equations provide eGFR indexed to body surface area (BSA) (i.e., in mL/min/1.73 m^2), whereas CG calculates eCL_{cr} as an absolute value (i.e., in mL/min). Therefore, reported eGFR values can differ significantly from eCL_{cr} if congruent units are not achieved by de-indexing for BSA (i.e., converted to an absolute value by multiplying by patient BSA/1.73 m^2), especially for patients of extreme body size.[51,52] Potential discordance between medication dosing recommendations based on these equations is well established.[51,53-55] Average discordance rates between eGFR equations and CG vary between 10% and 40%. This illustrates that the kidney function-estimating equation used for medication selection and dosing can have important clinical consequences on pharmacotherapy.[56]

Although quantitative assessment of kidney function is a crucial consideration, the output of kidney function-estimating equations should not be the sole determinant for pharmacotherapeutic decision making. Renal dose adjustment should be guided by clinical judgment, including an assessment of the risk-benefit ratio of the medication being prescribed, a complete clinical picture of the patient, and a thorough understanding of the limitations and implications of the various kidney function-estimating equations.[51] The ultimate goal of kidney function assessment and renal dose adjustment of medications is optimized and personalized pharmacotherapy.

Medication Dosing Information Resources

5 The 1998 FDA guidance on Pharmacokinetics in Patients with Impaired Renal Function were the first official guidelines addressing when and how to conduct pharmacokinetic and pharmacodynamic studies of a new medication in patients with impaired kidney function.[57] The 1998 guidance recommended that renal pharmacokinetic studies be conducted for medications with a narrow therapeutic index, medications that are primarily renally excreted, and medications for which the parent drug or active metabolite has high hepatic clearance and significant plasma protein binding. Furthermore, the guidance recommended assessing kidney function using CL_{cr} or serum creatinine (SCr) values.[57] The most recent 2020 draft guidance expands the recommendations of when to conduct renal pharmacokinetic studies to include medications that are predominantly cleared by nonrenal routes. Additionally, the use of eGFR, as calculated by a contemporary GFR-estimating equation, is preferred to assess kidney function.[58] The adoption of the FDA guidance has resulted in increased frequency of renal pharmacokinetic studies and improved availability of renal dosing recommendations, especially for medications with predominantly renal elimination. However, a lack of renal pharmacokinetic and dosing data persists for many medications, including oncology and antiviral agents and medications with $f_e < 0.3$, for which only 56% to 66% of medications approved from 1999 to 2010 have renal pharmacokinetic studies.[17]

The KDIGO guideline group recommends adjusting the dosage of medications in patients with CKD according to FDA- or EMA-approved labeling when such information is available. When this information is not available, the use of peer-reviewed literature is recommended to guide medication dosage adjustment.[16] These resources, along with other commonly used drug information sources such as Drug Prescribing in Renal Failure,[59] The Renal Drug Handbook,[60] Lexicomp,[61] Micromedex,[62] and the American Hospital Formulary Service Drug Information,[63] are excellent sources of information about a medication's pharmacokinetic characteristics. However, they are not without limitation and can yield marked variation in recommendations and the paucity of details of the methods used to generate the dosing advice (Table 67-3).[64,65] In addition, none of these sources consistently provide the explicit relationships of the pharmacokinetic parameters of interest (CL_T, elimination rate constant [k], and V_D) with a continuous index of kidney function (eCL_{cr} or eGFR). To find this information, one may need to identify the primary research study that assessed the medication's disposition, which can be a time-consuming process and difficult to carry out for each medication and patient combination in real time.

TABLE 67-3

Comparison of Secondary References Used for Medication Dosing in Patients with CKD

Resource	Pros	Cons
Aronoff's Drug Prescribing in Renal Failure[63]	• Exclusive focus on medication dosing in patients with CKD • Information provided for IHD, PD, CRRT • Tables include medication PK and dosage adjustment based on CL_{cr} (>50, 10-50, <10 mL/min [>0.83, 0.17-0.83, <0.17 mL/s]) • Tables for both adult and pediatric dosing provided • Concise, easy to use • References to primary literature provided	• Updated infrequently; information may not be current, newer medications may not be included • Some dosage recommendations are not feasible for dialysis patients (i.e., q 36 hours dosing interval)
The Renal Drug Handbook[64]	• Easy to access with a subscription • Contains information on clinical use of medications, PK, dose in normal kidney function, dose adjustment in CKD, drug interactions and administration • Specific to CKD patients	• Updated every few years; information may not be current, newer medications may not be included • References not provided
Lexicomp[65]	• Easy to access with a subscription • Easy to navigate • Concise information • Dose adjustment in CKD provided (including HD and PD)	• May be difficult to navigate • No specific focus on CKD patients • References to primary literature for dosing not provided
Micromedex[66]	• Easy to access with a subscription • Comprehensive, detailed information (both "in-depth" and "quick") • Dose adjustment in CKD provided (including HD and PD)	• May be difficult to navigate • No specific focus on CKD patients • References to primary literature for dosing not consistently provided
American Hospital Formulary Service (AHFS)[67]	• Easy to access with a subscription • Detailed medication monographs • "Dosage in Renal and Hepatic Impairment/Special Populations" section for each medication listed • Online version updated regularly, print version updated yearly	• Hard copy version can be difficult to navigate, cumbersome • Information on dose adjustment in CKD is minimal • No specific focus on CKD patients • References to primary literature for dosing not provided

CKD, chronic kidney disease; CL_{cr}, creatinine clearance; CRRT, continuous renal replacement therapy; HD, hemodialysis; IHD, intermittent hemodialysis; PD, peritoneal dialysis; PK, pharmacokinetics.

Data from References 59-63.

MEDICATION DOSAGE REGIMENS FOR NONDIALYSIS CKD PATIENTS

6 Dosage regimen design in CKD patients is dependent on the pharmacodynamic/pharmacokinetic characteristics of the medication, the patient's

degree of residual kidney function, and their overall clinical condition. The initial or "loading" dose for CKD patients should be the same as the dose recommended for those with normal kidney function unless the medication's V_D is known to be altered in CKD or a concomitant disease.[11] If V_D is increased, then the dose should be increased proportionally (see Table 67-1). Rapid achievement of therapeutic drug concentrations is important in many patient care situations and thus it is often better to start therapy aggressively rather than conservatively.

If available, maintenance dosage regimen guidelines for CKD patients in FDA- or EMA-approved product labeling should be the foundation for ongoing therapy.[16] Approved product labeling typically includes dose adjustment recommendations for ranges of kidney function. These ranges represent mild (eCL_{Cr} 60-90 mL/min or eGFR 60-90 mL/min/1.73 m^2), moderate (eCL_{Cr} 30-59 mL/min or eGFR 30-59 mL/min/1.73 m^2), and severe (eCL_{Cr} <30 mL/min or eGFR <30 mL/min/1.73 m^2) CKD (see Chapter 62, "Chronic Kidney Disease").[66] Each of these categories encompasses a broad range in kidney function, and thus the recommended dosage regimen may not be optimal for all patients whose kidney function lies within a given kidney function category.

Quantifying the Relationship Between Kidney Function and Medication Clearance

If FDA- or EMA-approved product labeling information is not available or if there is marked variance between these two agencies' recommendations, a stepwise approach for designing a dosage regimen for a patient with CKD can be used. In either case, the design of the optimal dosage regimen is dependent on the availability of an accurate characterization of the relationship between the pharmacokinetic parameters of the medication and kidney function and an accurate assessment of the patient's kidney function.

The "Dettli Method" is a graphical means to generate medication dosing recommendations based on the linear relationship between the elimination rate constant of a renally cleared medication and a patient's creatinine clearance:

$k = k_{NR} + (\alpha \times CL_{cr})$k = kNR + (α×CLcr)

where k is the elimination rate constant of the medication based on a first-order one-compartment model, k_{NR} is the nonrenal elimination rate constant, and α is a constant relating the renal drug elimination rate constant to the patient's creatinine clearance (CL_{cr}).[67] This approach assumes that the overall elimination rate constant (k), relating to CL_T, declines linearly with CL_{cr}, and that the nonrenal elimination rate constant (k_{NR}), relating to CL_{NR}, remains constant as kidney function declines. While the first assumption generally holds true for medications that are mainly renally cleared, the second assumption is flawed, as CL_{NR} can be altered in CKD.[8-15] The relationship between CL_T and CL_{cr} for selected medications is depicted in Table 67-4. This information, along with the patient's eCL_{cr} or eGFR, is the foundation upon which a therapeutic regimen to attain the desired medication concentration-time profile and ultimately the therapeutic outcome can be formulated when renal dosing information is not provided in the approved product labeling information.

TABLE 67-4

Relationship Between CL_{cr} and CL_T of Selected Medications

Medication	Total Systemic Clearance[a]
Acyclovir	$CL_T = 3.37\ (CL_{cr}) + 0.41$
Amikacin	$CL_T = 0.6\ (CL_{cr}) + 9.6$
Aztreonam	$CL_T = 0.8\ (CL_{cr}) + 26.6$
Cefazolin	$CL_T = 0.34\ (CL_{cr}) + 6.6$
Ceftazidime	$CL_T = 1.15\ (CL_{cr}) + 10.6$
Ciprofloxacin	$CL_T = 2.83\ (CL_{cr}) + 363$
Digoxin	$CL_T = 0.88\ (CL_{cr}) + 23$
Ganciclovir	$CL_T = 1.24\ (CL_{cr}) + 8.57$
Gentamicin	$CL_T = 0.983\ (CL_{cr})$
Imipenem	$CL_T = 1.42\ (CL_{cr}) + 54$
Lithium	$CL_T = 0.20\ (CL_{cr})$
Ofloxacin	$CL_T = 1.04\ (CL_{cr}) + 38.7$
Piperacillin	$CL_T = 1.36\ (CL_{cr}) + 1.50$
Tobramycin	$CL_T = 0.801\ (CL_{cr})$
Vancomycin	$CL_T = 0.69\ (CL_{cr}) + 3.7$

CL_T, total systemic clearance; CL_{cr}, creatinine clearance.

[a]Clearance in mL/min can be converted to mL/s through multiplication by 0.0167.

However, the linear relationship of kinetic parameters to eGFR or eCL_{cr} is often not explicitly reported. In this case, then the CL_T or k for CKD patients can be estimated using the method of Rowland and Tozer, provided that f_e for subjects with normal kidney function is known.[18] This approach assumes that the changes in CL_T and k are proportional to eCL_{cr}, that CKD does not alter the medication's metabolism, that any metabolites that are formed are inactive and nontoxic, and that the medication obeys first-order (linear) one-compartment kinetic principles. If these assumptions are true, which is rarely the case, then the dosage-adjustment factor (Q) can be calculated as:

$Q = 1 - [f_e(1 - \mathrm{KF})]$ $Q = 1 - [fe(1 - KF)]$

where KF is the ratio of the patient's kidney function (i.e., eCL_{cr} or eGFR) to the assumed normal value of 120 mL/min. Thus, for a medication that is

85% eliminated renally unchanged in a patient who has an eCL_{cr} of 10 mL/min, *Q* would be:

$$\begin{aligned} Q &= 1-(0.85[1-(10/120)]) \\ &= 1-(0.85[1-0.083]) \\ &= 1-0.78 \\ &= 0.22 \end{aligned}$$

Q=1−(0.85[1−(10/120)])=1−(0.85[1−0.083])=1−0.78=0.22

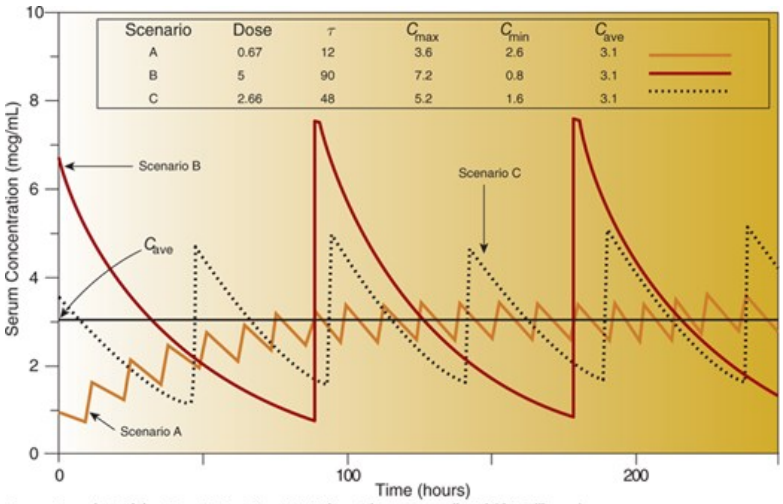
Designing Adjusted Renal Dosage Regimens

In order to determine the best method for dosage regimen adjustment, a regimen goal must be defined.[10,11] The goal may be pharmacokinetic (maintenance of a similar peak, trough, or average steady-state drug concentration) or pharmacodynamic (time above the MIC [e.g., cephalosporins] or the ratio of the *AUC* relative to the MIC [e.g., fluoroquinolones]). If there is a strong relationship between peak concentration and clinical response (e.g., aminoglycosides) or toxicity (e.g., phenobarbital and phenytoin), then the attainment of specific target values is critical for optimal therapeutic outcomes. If, however, no specific target values for peak or trough concentrations have been reported, then a regimen goal of attaining the same average steady-state concentration is likely to be appropriate.

The options to attain the desired average steady-state concentration profile in CKD patients are to either decrease the dose or increase the dosing interval (τ). If the dose is decreased and the dosing interval remains unchanged, then the average steady-state concentration will be unchanged but the peaks will be lower and the troughs will be higher. Conversely, if the dosing interval is increased and the dose remains unchanged, then the average steady-state, peak, and trough concentrations in the patient with CKD will be similar to those in the patient with normal kidney function (Fig. 67-1).[68] Increasing the dosing interval is the approach used most commonly to adjust dosage regimens in patients with CKD because it translates into a lower daily medication burden in these patients. Moreover, it is likely to yield cost savings as a result of a reduction in pharmacy and nursing time for preparation and administration of fewer (less frequent) doses, as well as a reduction in the corresponding supplies. Lastly, it is important to note that occasionally both the dose and dosing interval may need to be changed for pragmatic reasons (i.e., to allow the administration of a clinically practical dose [500 mg vs a calculated value of 487 mg] or dosing interval [administer every 12 hours vs every 17 hours]).

FIGURE 67-1

Although the average steady-state concentrations (C_{ave}) are identical regardless of which dosage-adjustment strategy one decides to implement, the concentration-time profile will be markedly different if one changes the dose and maintains the dosing interval (τ) constant (*Scenario A*), versus changing the dosing interval and maintaining the dose constant (*Scenario B*) or changing both (*Scenario C*).



Source: Joseph T. DiPiro, Gary C. Yee, Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 12e*

If the relationships between the pharmacokinetic parameters of the medication and kidney function are known (i.e., equations are available such as those depicted in Table 67-4), then the change in dose and/or dosing interval for a patient with a given kidney function can be calculated and a dosage regimen adjustment can be designed using a stepwise approach. CL_T is calculated for a patient with normal kidney function (CL_{cr} or eGFR = 120 mL/min) and a patient with CKD based on available equations describing the quantitative relationship between CL_T and CL_{cr} or eGFR (as presented in

Table 67-4). In this situation, the dosage-adjustment factor (Q) is calculated as the ratio of the estimated k or CL of the patient with CKD relative to a subject with normal kidney function. The Q is then used to determine the adjusted dose or dosing interval for a patient with CKD, as follows:

$$D_{CKD} = D_{norm} \times Q \qquad \tau_{CKD} = \tau_{norm}/Q$$

DCKD=Dnorm×QτCKD=τnorm/Q

where D_{CKD} is the adjusted dose for a patient with CKD, D_{norm} is the standard dose for a patient with normal kidney function, τ_{CKD} is the adjusted dosing interval for a patient with CKD, τ_{norm} is the standard dosing interval for a patient with normal kidney function, and Q is the dosage-adjustment factor. The strategy for dosing adjustment (i.e., decrease the dose or increase dosing interval) is chosen and the corresponding dosing interval or dose is calculated.

An example of this process is illustrated in Table 67-5 for ciprofloxacin, a commonly used antibiotic for the treatment of infections in CKD and dialysis patients. Ciprofloxacin is a concentration-dependent antibiotic, and thus the peak concentration and *AUC* determine its efficacy. Therefore, extending the interval but keeping the same dose allows for peak concentrations in CKD patients similar to those seen in normal kidney function, allowing for this pharmacodynamic action to be achieved without accumulation of medication that could cause dose-dependent toxicities.

TABLE 67-5

Stepwise Approach to Calculating a Dosage Regimen Based on a Medication's Pharmacokinetic Properties and a Patient's Kidney Function

	Steps	Calculation Examples with Ciprofloxacin
Step 1	Calculate total systemic clearance of medication in an individual with normal kidney function (CL_{norm}); CL_{cr} = 120 mL/min	$CL_{norm} = [2.83 (CL_{cr})] + 363$ $CL_{norm} = [2.83(120)] + 363$ CL_{norm} = 702.6 mL/min
Step 2	Calculate total systemic clearance of medication in a patient with CKD (CL_{CKD})	In patient with CL_{cr} = 15 mL/min $CL_{CKD} = [2.83(CL_{cr})] + 363$ $CL_{CKD} = [2.83(15)] + 363$ CL_{CKD} = 405.5 mL/min
Step 3	Calculate the dosage-adjustment factor (Q) for a patient with CKD as the ratio of the CL of the patient with CKD relative to an individual with normal kidney function	$Q = CL_{CKD}/CL_{norm}$ Q = 702.6/405.5 Q = 0.58
Step 4	Calculate the maintenance dose (D_{CKD}) or adjusted dosing interval (τ_{CKD}) in a patient with CKD; D_{norm} = normal dose; τ_{norm} = normal dosing interval	D_{norm} = 500 mg; τ_n = 12 h $D_{CKD} = D_{norm} \times Q$ D_{CKD} = 500 mg × 0.58 D_{CKD} = 290 mg $\tau_{CKD} = \tau_{norm}/Q$ τ_{CKD} = 12/0.58 τ_{CKD} = 20.7 h
Step 5	Choose dosing adjustment: Option A. Maintain D_{norm} and use τ_{CKD} Option B. Maintain τ_{norm} and use D_{CKD}	Dosing adjustments: Option A. 500 mg every 21 hr Option B. 290 mg every 12 hr
Step 6	Determine adjusted dosing regimen based on Option A using a practical dosing interval	D_{norm} = 500 mg; τ_{CKD} = 21 h *Practical* τ = 24 h (selected to limit missed doses)
Step 7	Recommend dosing regimen (dependent on product availability and limited risk of missed doses)	500 mg every 24 h

CL_{cr}, creatinine clearance.

Creatinine clearance in mL/min can be converted to mL/s through multiplication by 0.0167. Clearance in mL/min/1.73 m^2 can be converted to mL/s/m^2 through multiplication by 0.00963.

If the V_D of a medication is significantly altered in CKD patients or if one desires to attain a specific maximum or minimum concentration, the estimation of a dosage regimen becomes more complex. If the relationship between V_D and CL_{cr} has been characterized, then V_D may be estimated. If one assumes that a one-compartment linear model can describe the medication, the predicted V_D may then be used with the predicted k of the medication to yield an adjusted-dosing interval and IV dose:

$$\tau_{CKD} = (-1/k)[\ln(C_{min}/C_{max})] \quad \tau CKD=(-1/k)[\ln(Cmin/Cmax)]$$
$$D_{CKD} = V_D \times (C_{max} - C_{min}) \quad DCKD=VD\times(Cmax-Cmin)$$

where τ_{CKD} is the adjusted dosing interval for a patient with CKD and D_{CKD} is the adjusted dose for a patient with CKD. These principles have been used to derive dosage recommendations for many commonly used medications for CKD patients. It should be noted, however, that in most dosing guidelines, the "usual" dose or dose for "normal kidney function" represents eGFR greater than 50 mL/min/1.73 m^2. This assumption, however, could lead to dosing errors for patients with eGFRs of 60 mL/min/1.73 m^2 versus 90 mL/min/1.73 m^2 versus 130 mL/min/1.73 m^2. Augmented renal clearance, defined as CL_{cr} greater than 130 mL/min/1.73 m^2, has been associated with subtherapeutic antibiotic concentrations and outcomes in critically ill patients when standard doses of antibiotics were administered.[69] Clinicians should be aware of the potential to underdose critically ill patients with documented augmented kidney function and thus should consider the use of higher doses, especially for antibiotics and antivirals.

MEDICATION DOSAGE REGIMENS FOR DIALYSIS PATIENTS

The rationale and approaches for delivery of renal replacement therapy to patients with ESKD are described in Chapter 64, "Hemodialysis and Peritoneal Dialysis." This section will describe medication dosing regimens for patients on traditional HD, peritoneal dialysis, and alternative HD modalities, including short-daily hemodialysis (SDHD) and nocturnal hemodialysis (NHD). Several forms of continuous renal replacement therapy in clinical use today and corresponding approaches to individualize dosage regimens are described in Chapter 61, "Acute Kidney Injury."

Hemodialysis

Principles of Hemodialytic Clearance of Medications

The impact of HD on a patient's pharmacotherapy is dependent on several factors, including the physicochemical characteristics of the medication and the dialysis prescription. Medication-related factors that affect dialyzability include molecular weight, degree of protein binding, and V_D.[19] The permeability of a dialysis filter for medication depends on the composition of the filter and the molecular weight of the medication. The majority of dialysis filters in use in North America up until the mid-1990s were composed of cellulose, cellulose acetate, or regenerated cellulose (cuprophane) and were generally impermeable to medications with a molecular weight >1,000 Da.[16] Dialysis membranes in the 21st century ("high-flux" dialysis membranes) are predominantly composed of semisynthetic or synthetic materials (e.g., polysulfone, polymethylmethacrylate, or polyacrylonitrile), have larger pore sizes, and more closely mimic the filtration characteristics of the human kidney. This allows for the passage of most solutes, including medications that have a molecular weight up to 20,000 Da, causing larger medications to be more easily removed with high flux dialyzers.[16] Some medications that are cleared in high-flux dialysis, but not through conventional dialysis, include vancomycin, carbamazepine, cisplatin, enoxaparin, ranitidine, valproic acid, sorafenib, and tramadol. The effect of HD on drug disposition is rarely reevaluated after it is initially reported; therefore, information for medications that were developed prior to the advent of high-flux dialysis membranes probably represents an underestimation of the impact of HD on a medication's disposition. Therapeutic drug monitoring for medications such as aminoglycosides and vancomycin should also be performed to ensure adequate dosing for patients on HD. Medications that are highly protein bound (i.e., $f_u < 0.10$) are not well dialyzed because both of the principal drug-binding plasma proteins, α1-acid glycoprotein and albumin, have a high molecular weight. Finally, medications that are widely distributed, with V_D greater than 2 L/kg, are poorly removed by HD.

The dialysis prescription can dramatically affect the total clearance of a medication.[95] HD can occur in a number of clinical settings, including acute management of AKI, intermittent three times a week, daily for an extended period, or some combination thereof for the management of category G5 CKD patients. The primary factors that vary between patients are the composition of the dialysis filter, the filter surface area, the blood, dialysate and ultrafiltration flow rates, and whether or not the dialysis unit reuses the dialysis filter.[16]

Overall, the impact of HD on pharmacotherapy is highly variable. One cannot assume that a certain percentage of a medication is removed with each

dialysis session and an "all" or "none" approach regarding the dialyzability of a medication is insufficient information to make therapeutic decisions. Characteristics of the dialysis procedure that were utilized in the drug study, such as membrane composition and surface area and blood and dialysis flow rates, are critical parameters that should be known before one uses the published HD clearance data to prospectively design a medication dosing regimen for an HD patient.

Prospective Monitoring of Medication Concentrations

If medication concentrations can be measured in the clinical setting, the quantitative impact of HD on drug disposition can be calculated in one of the several ways.[19] The most commonly utilized means for assessing the effect of HD is to calculate the dialyzer clearance (CL_D) of the medication. The CL_D^pCLDp from blood can be calculated as:

$CL_D^p = Q_p[(A_p - V_p)/A_p]$CLDp = Qp[(Ap–Vp)/Ap]

where Q_b is the blood flow through the dialyzer and Q_p is the plasma flow, which equals Q_b (1 − hematocrit); A_p is the plasma concentration of medication entering the dialyzer, and V_p is the plasma concentration of the medication leaving the dialyzer. This clearance calculation most accurately reflects dialysis drug clearance as most medications do not extensively penetrate red blood cells or bind to formed blood elements. However, for medications that readily partition into and out of erythrocytes, this equation would likely underestimate HD clearance. Furthermore, one must keep in mind that venous plasma concentrations may be artificially high and CL_D^pCLDp will be low if plasma water is removed from the blood at a faster rate than the medication. This tends to occur when extensive ultrafiltration is performed simultaneously with diffusion during dialysis.[16,19]

The following principles may be used to generate a medication dosage regimen recommendation for HD patients, if none is available in product labeling or other sources, by using a value of CL_D.[16,19] Because clearance terms are additive, the total clearance during dialysis can be calculated as the sum of the patient's underlying residual systemic clearance stemming from the patient's remaining renal clearance and nonrenal clearance during the interdialytic period (CL_{RES}) and dialyzer clearance (CL_D):

$CL_T = CL_{RES} + CL_D$CLT = CLRES + CLD

The half-life during the period between dialysis treatments and during dialysis can then be calculated from the following relationships using an estimate of the medication's V_D (see Table 67-2)[19]:

$t_{1/2,\,\text{off HD}} = 0.693(V_D/CL_{RES})$
$t_{1/2,\,\text{on HD}} = 0.693\,(V_D/CL_{RES} + CL_D)$ t1/2, off HD=0.693(VD/CLRES)t1/2, on HD=0.693 (VD/CLRES+ CLD)

Once the key pharmacokinetic parameters have been estimated/calculated, they may be used to simulate the plasma concentration-time profile of the medication for the individual patient and then one can ascertain how much medication to administer and when. This approach to personalizing pharmacotherapy can be accomplished in a stepwise fashion assuming first-order elimination of the medication and a one-compartment model.

CLINICAL CASE EXAMPLE: Personalizing Pharmacotherapy for a Hemodialysis Patient

A 54-year-old critically ill woman with ESKD was transferred to a medical intensive care unit from the general medical unit, where she was febrile with a temperature of 39°C (102.2°F). Her weight was 64 kg (141 lb) and her height was 65 in (165 cm). She had a residual CL_{cr} of 5 mL/min (0.083 mL/s), and was receiving high-flux hemodialysis (F80 polysulfone dialyzer) for 4 hours on Mondays, Wednesdays, and Fridays. She was started on vancomycin for a methicillin-resistant *Staphylococcus aureus* (MRSA) catheter-associated bacteremia and her first dose of 1,000 mg was administered at the end of her HD treatment. The first step is to estimate this patient's pharmacokinetic parameters of vancomycin using known population data (Table 67-1) and equations (Table 67-4). The V_D in this patient can be estimated to be 54.4 L (0.85 L/kg × 64 kg). Her underlying residual systemic clearance (CL_{RES}) of vancomycin is estimated from the relationship between CL_T and kidney function (where CL_T = [0.69 × CL_{cr}] +3.7) and is 7.15 mL/min (0.12 mL/s) or 0.43 L/h. The *k* can be approximated as:

$k = CL_{RES}/V_D$
$= 0.43\,\text{L/h} / 54.4\,\text{L}$k=CLRES/VD=0.43 L/h / 54.4 L=0.0079 h−1
$= 0.0079\,\text{h}^{-1}$

The HD clearance of vancomycin (CL_D) is dependent on the dialyzer and a value of 120 mL/min (2 mL/s; 7.2 L/hr) is a reasonable estimate for this dialyzer.[20]

One can now predict what the plasma concentrations of vancomycin will be over the next 24 to 48 hours, assuming the infusion time for the medication (t') was 1 hour. The concentration at the end of the 1-hour infusion (C_{max}) would be:

$$\begin{aligned} C_{max} &= \frac{(\text{Dose}/t')}{\text{CL}_{\text{RES}}}(1 - e^{-kt'}) \\ &= \frac{(1.000\,\text{mg/h})}{(0.43\,\text{L/h})}(1 - e^{-(0.0079)(1)}) \\ &= (2,325.58\,\text{mg/L})(0.0078) \\ &= 18.1\,\text{mg/L} \end{aligned}$$

Cmax=(Dose/t′)CLRES(1−e−kt′)=(1.000 mg/h)(0.43 L/h)(1−e−(0.0079)(1))=(2,325.58 mg/L)(0.0078)=18.1 mg/L

The plasma concentration prior to the next dialysis session (C_{bD}), which is 44 hours away can be calculated as:

$$\begin{aligned} C_{bD} &= C_{max} \times e^{-(\text{CL}_{\text{RES}}/V_D)\times t} \\ &= 18.1 \times e^{-0.0079\times 44} \\ &= 12.8\,\text{mg/L} \end{aligned}$$

CbD=Cmax×e−(CLRES/VD)×t=18.1×e−0.0079×44=12.8 mg/L

and the concentration 4 hours later after dialysis (C_{aD}) can be calculated as:

$$\begin{aligned} C_{aD} &= C_{bD} \times e^{-[(CL_{RES} + CL_D + CL_D/V_D)]\times t} \\ &= 12.8 \times e^{-[(0.43+7.2)/54.4]\times 4} \\ &= 12.8 \times e^{-0.14\times 4} \\ &= 7.3\,\text{mg/L} \end{aligned}$$

CaD=CbD×e−[(CLRES+CLD+CLD/VD)]×t=12.8×e−[(0.43+7.2)/54.4]×4=12.8×e−0.14×4=7.3 mg/L

On the basis of these data, the second dose, which should be administered after the second dialysis session, was increased in order to maintain vancomycin trough concentrations between 15 and 20 mg/L (10-14 µmol/L) for an MRSA catheter-associated bacteremia, as this is likely to attain the *AUC* target of 400 to 600 mg·h/L in the previous 24 hours.[70,71] The patient received a vancomycin dose of 1,500 mg 4 hours after the end of the second dialysis session. The increase or change in serum concentration (ΔC) at the end of this 1-hour infusion can thus be estimated:

$$\begin{aligned} \Delta C &= \frac{(\text{Dose}/t')}{CL_{\text{RES}}}(1 - e^{-kt'}) \\ &= \frac{(1,500\,\text{mg/h})}{0.43\,\text{L/h}}(1 - e^{-((0.0079)1)}) \\ &= (3,488.4\,\text{mg/L})(0.0078) \\ &= 27.2\,\text{mg/L} \end{aligned}$$

ΔC=(Dose/t′)CLRES(1−e−kt′)=(1,500 mg/h)0.43 L/h(1−e−((0.0079)1)=(3,488.4 mg/L)(0.0078)=27.2 mg/L

Thus, the C_{max} would be approximately 34.5 mg/L (24 µmol/L), the sum of the residual concentration from the first dose of 7.3 mg/L (5 µmol/L) and the ΔC of 27.2 mg/L (18.8 µmol/L). The plasma concentration prior to the third dialysis session (C_{bD}), which is 40 hours away can be estimated as:

$$\begin{aligned} C_{bD} &= C_{max} \times e^{(\text{CL}_{\text{RES}}/V_D)\times t} \\ &= 34.5\,\text{mg/L} \times e^{-0.0079\times 40} \\ &= 25.2\,\text{mg/L} \end{aligned}$$

CbD=Cmax×e(CLRES/VD)×t=34.5 mg/L×e−0.0079×40=25.2 mg/L

and the concentration 4 hours later after the third dialysis (C_{aD}) can be estimated as:

$$\begin{aligned} C_{aD} &= C_{bD} \times e^{-[(CL_{RES}+CL_D)/V_D]\times t} \\ &= 25.2 \times e^{-[(0.43+7.2)/54.4]\times 4} \\ &= 25.2 \times e^{-0.14\times 4} \\ &= 14.4\,\text{mg/L} \end{aligned}$$

CaD=CbD×e−[(CLRES+CLD)/VD]×t=25.2×e−[(0.43+7.2)/54.4]×4=25.2×e−0.14×4=14.4 mg/L

This higher dose would be considered to have achieved concentrations that are too high since the lowest value during the majority of the dosing interval exceeded 25.2 mg/L (17.1 µmol/L). The dose required to maintain vancomycin trough concentrations between 15 and 20 mg/L (10-14 µmol/L) should be determined.

For medications with a narrow therapeutic index (e.g., vancomycin, phenytoin, and gentamicin), therapeutic drug monitoring (e.g., plasma concentration measurements and dialyzer clearance estimation) should be utilized to guide medication dosing.[19] The ultimate reason for measuring the plasma concentrations of antibacterial agents is to individualize the patient's dosage regimen to achieve a bacteriologic cure while preventing adverse effects and preserving residual kidney function. Vancomycin dosing is primarily based on attaining desired trough concentrations, usually between 15 and 20 mg/L (10-14 µmol/L) as this is likely to attain the target *AUC* of 400 to 600 mg·hr/L in the previous 24 hours.[70,71] It is common practice to administer medications post-dialysis on the premise that it is desirable to minimize the loss of medication that would result from dialyzer clearance. For example, the administration of traditional doses of tobramycin (1.5 mg/kg) or vancomycin (1,000 mg) during dialysis has been associated with markedly lower *AUC*s than those observed when the same dose was administered post-dialysis; consequently, higher dosage regimens are usually necessary to compensate for the additional loss of medication during the dialysis procedure. However, there are clinical scenarios when pre-dialysis or intradialytic medication administration may be optimal. Medications for pain may be given on a precise schedule and thus would be administered

irrespective of the time on dialysis. Furthermore, it may be optimal to administer some medications, such as aminoglycosides[72,73] and vancomycin,[74,75] during or immediately prior to the start of a dialysis treatment. For example, pre-dialysis or intradialytic aminoglycoside dosing may obtain similar peak concentrations, a prime indicator of efficacy, but lower *AUC*, a correlate to ototoxicity and nephrotoxicity, compared to post-dialysis dosing.[72] Performing HD immediately after dosing might also be a good option for several anticancer medications. The pre-dialysis administration of a normal dose makes sense when the patient undergoes HD 2 to 12 hours later. This strategy delivers the desired maximum plasma concentration effect while minimizing patient exposure to the toxic drug or metabolite effects.[76,77]

Peritoneal Dialysis

Peritoneal dialysis, like other dialysis modalities, has the potential to affect drug disposition; however, personalizing pharmacotherapy is often less complicated in these patients as a result of the limited clearances of medications achieved with this procedure (see Chapter 64, "Hemodialysis and Peritoneal Dialysis"). In general, HD is more effective in removing medications than peritoneal dialysis, such that if a medication is not removed by HD, it is unlikely to be significantly removed by peritoneal dialysis.

Many of the factors that are important in determining medication dialyzability for other treatment modalities pertain to peritoneal dialysis as well.[78,79] Factors that influence medication dialyzability by peritoneal dialysis include drug-specific characteristics such as molecular weight, solubility, degree of ionization, protein binding, and V_D. The intrinsic properties of the peritoneal membrane that affect medication removal include blood flow and peritoneal membrane surface area, which is approximately equal to the body surface area. There is an inverse relationship between peritoneal clearance of medications and molecular weight, protein binding, and V_D. In addition, medications that are ionized at physiologic pH will diffuse across the membrane more slowly than unionized compounds.[78,79]

Peritoneal dialysis, in current practice, is often prescribed to attain a urea clearance of approximately 10 mL/min (0.17 mL/s), so it is unlikely to significantly impact the *CL* of any medication. In addition, since most medications have a larger molecular size than urea, their resultant *CL* will likely be even lower: probably between 5 and 7.5 mL/min (0.08-0.13 mL/s). Therefore, medication dosing recommendations for the management of conditions other than peritonitis, reported for patients with estimated CL_{cr} or GFR of 10 to 15 mL/min (0.17-0.25 mL/s), are likely suitable for patients receiving peritoneal dialysis.[16]

Alternative Hemodialysis Modalities

Short-daily and nocturnal HD are two alternative HD techniques. Both modalities are administered 5 to 6 days a week but differ primarily in the duration of the treatment and blood-flow rate.[80] Overall small solute removal is more efficient if the frequency of HD is increased. Therefore, SDHD and NHD therapies yield different clearance values compared to intermittent three times per week HD. Furthermore, prolonged HD, such as in the case of NHD, results in less rebound of medication concentrations after the termination of dialysis. This likely occurs because the rate of transfer from the peripheral to central compartment relative to the rate of diffusive removal is lower. Therefore, careful monitoring of pharmacotherapy is necessary when these newer modalities are used to avoid potential errors in designing medication dosing regimens.

Nocturnal Hemodialysis

NHD is performed over 6 to 8 hours on 5 to 6 nights per week.[80] There is a paucity of information related to medication dosing with this modality; however, the principles of medication dosing discussed above with intermittent HD can also be applied here. Although there is an increase in dialysis hours, which would suggest an increase in medication removal, the blood and dialysate flow rates are slower and thus clearance per unit of time will be less. This has been demonstrated with cefazolin where the cefazolin clearance during NHD was slightly lower (*CL* = 1.65 L/hr) than during high-flux intermittent HD (*CL* = 1.85 L/hr); however, a greater percentage of cefazolin was removed in 8 hours of NHD (80%) than conventional 4-hour high-flux HD (60%).[81]

Short-Daily Hemodialysis

SDHD involves 2 to 3 hours of dialysis performed 5 to 6 days per week.[80] As in the case with NHD, there is also limited information on medication dosing with this modality; however, the general principles of medication dosing for HD also apply here. In SDHD, the number of dialysis sessions per week and

blood and dialysate flow rates are similar to intermittent HD, which may suggest similar medication removal. However, for certain medications (smaller size and decreased V_D, and protein binding) removal may be increased. For example, the cefazolin clearance rate in SDHD is slightly higher than the value observed during high-flux intermittent HD; the amount of cefazolin removed in 2 hours of SDHD is similar to that after 4 hours of high-flux HD.[82] Therefore, the same amount of medication given over the entire week for patients on intermittent HD could also be given to patients on SDHD but in smaller amounts administered more frequently. For instance, in intermittent HD, the cefazolin dose is typically 2 g IV after each HD for a total of 6 g/week; whereas in SDHD, the dose would be 1 g IV daily (i.e., for 6 days) after each HD.

CONCLUSION

Patients with CKD often exhibit changes to pharmacokinetics and pharmacodynamics, and medication dosage regimen adjustment is often warranted in these patients. When available, the utilization of FDA or EMA medication dosage recommendations in official prescribing information should be used for the initiation of therapy in most clinical situations. However, when these guidelines are unavailable for the relevant clinical setting, the use of pharmacokinetic principles in conjunction with reliable population pharmacokinetic estimates may be used to determine the optimal medication dosage regimen. Prospective monitoring of serum concentrations for medications with a narrow therapeutic index should be undertaken whenever clinical therapeutic monitoring tools are available. The ultimate goal of medication dosage regimen adjustment in CKD is to individualize and optimize pharmacotherapeutic outcomes in this population to maximize therapeutic efficacy while minimizing unnecessary toxicity.

ABBREVIATIONS

α	constant relating the renal drug elimination rate constant to creatinine clearance
A_b	concentration of medication in blood going into the dialyzer (arterial side)
AKI	acute kidney injury
A_p	concentration of medication in plasma going into the dialyzer (arterial side)
AUC	area under the plasma concentration-time curve
$AUC_{0\text{-}t}$	the area under the predialyzer plasma concentration-time curve during hemodialysis
BCRP	breast cancer resistance protein
BSA	body surface area
Δ*C*	change in plasma concentration
C_{aD}	plasma concentration after dialysis
C_{bD}	plasma concentration prior to the next dialysis session
CG	Cockcroft–Gault
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration Equation
CL	clearance

CL_D^bCLDb	dialyzer clearance from blood
CL_{CKD}	clearance of a medication in patients with CKD
CL_{cr}	creatinine clearance
CL_D	dialyzer clearance
CL_{filt}	renal filtration clearance
CL_{norm}	clearance of a medication in patients with normal kidney function
CL_{NR}	nonrenal clearance
CL_D^pCLDp	dialyzer clearance from plasma
CL_R	renal clearance
$CL_{reabsorption}$	renal tubular reabsorption
CL_{RES}	residual clearance in a dialysis patient
$CL_{secretion}$	renal tubular secretion clearance
CL_T	total clearance
$C_{reported}$	patient's total phenytoin concentration reported by the laboratory
C_{max}	peak or maximum concentration
C_{min}	trough or minimum concentration
$C_{normal\ binding}$	total phenytoin concentration that would be observed if a patient had normal protein binding
C_{ss}	average steady-state plasma concentration
CYP	cytochrome P450
D_{CKD}	maintenance dose for a patient with CKD
D_{norm}	dose for a patient with normal kidney function
eCL_{cr}	estimated creatinine clearance
eGFR	estimated glomerular filtration rate
EMA	European Medicine Agency
ESKD	end-stage kidney disease

FDA	Food and Drug Administration
f_e	fraction of medication eliminated unchanged in the urine
f_u	fraction of medication unbound to plasma proteins
GFR	glomerular filtration rate
GI	gastrointestinal
HD	hemodialysis
IV	intravenous
k	elimination rate constant
k_a	absorption rate constant
k_{NR}	nonrenal elimination rate constant
KDIGO	Kidney Disease: Improving Global Outcomes
KF	ratio of the patient's CL_{cr} to the assumed normal value of 120 mL/min (2 mL/s)
MATE	multidrug and toxin extrusion protein
MIC	minimum inhibitory concentration
mRNA	m ribonucleic acid
MRP	multidrug resistance protein
MRSA	methicillin-resistant *Staphylococcus aureus*
NHD	nocturnal hemodialysis
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCT	organic cation transporter
OCTN	organic cation and carnitine transporters
P-gp	P-glycoprotein
Q	kinetic parameter/dosage-adjustment factor
Q_b	blood flow through the dialyzer
Q_p	plasma flow through the dialyzer = Q_b (1 – hematocrit)

R	the total amount of medication recovered unchanged in the dialysate
SCr	serum creatinine
SDHD	short daily hemodialysis
t'	infusion time of medication
Δt	time in hours between two measured concentrations
$t_{1/2}$	half-life
$t_{1/2,\text{ on HD}}$	half-life during dialysis
$t_{1/2,\text{ off HD}}$	half-life off dialysis
τ_{CKD}	dosing interval in a patient with kidney failure
τ_{norm}	dosing interval in a patient with normal kidney function
t_{max}	time to peak concentration
UGT	uridine diphosphate-glucuronosyltransferase
V_{area}	volume of distribution area
V_b	blood concentration of medication leaving the dialyzer
V_β	volume of terminal phase (serum protein)
V_c	volume of the central compartment
V_D	volume of distribution
V_{ss}	volume of distribution at steady state

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SELF-ASSESSMENT QUESTIONS

1. Which of the following is a source of variability in absorption of medications in patients with CKD?
   A. Increased pre-systemic metabolism
   B. Delayed gastric emptying
   C. Increased gastric acidity
   D. Decreased renal clearance
2. Which of the following is a potential mechanism by which the volume of distribution of medications is increased in patients with chronic kidney disease?
   A. Decreased plasma protein binding
   B. Decreased tissue binding
   C. Increased fluid excretion
   D. Decreased nonrenal clearance
3. Increased concentrations of α1-acid glycoprotein leads to a reduction in plasma protein binding of _____ medications.
   A. Hydrophilic
   B. Lipophilic
   C. Acidic

D. Basic

4. Renal clearance of a medication is a composite of all of the following pathways EXCEPT:

   A. Absorption

   B. Glomerular filtration

   C. Reabsorption

   D. Secretion

5. Metabolites of drugs may be pharmacologically active and may accumulate in patients with impaired kidney function. Which of the following medications has an active metabolite that may accumulate and lead to toxicity in patients with CKD?

   A. Aspirin

   B. Canagliflozin

   C. Midazolam

   D. Morphine

6. Which of the following pathways is NOT a major contributor to nonrenal clearance of medications?

   A. Metabolism by cytochrome P450 (CYP) enzymes

   B. Metabolism by uridine diphosphate-glucuronosyltransferase (UGT) enzymes

   C. Transport by organic anion transporter polypeptides (OATP)

   D. Tubular secretion by the organic anion transporters (OATs)

7. References to primary literature are provided in which of the following sources of medication information?

   A. Aronoff's *Drug Prescribing in Renal Failure*

   B. *The Renal Drug Handbook*

   C. *Lexicomp*

   D. *American Hospital Formulary Service* (AHFS)

8. Which of the following statements regarding the Rowland and Tozer method for estimating the total body clearance (CL_T) of medications in patients with CKD is CORRECT?

   A. This method can be used for medications with known alternations in their metabolism among CKD patients.

   B. The fraction of the medication that is eliminated renally unchanged (fe) in subjects with normal kidney function must be known.

   C. It is applicable when the medication obeys nonlinear kinetic principles.

   D. The change in CL must be disproportional to CL_{cr}.

9. A patient with CKD who has a CL_{cr} of 20 mL/min (0.33 mL/s) is to receive an antibiotic that has a fe of 85%. Based on this information, calculate the kinetic parameter/dosage-adjustment factor (Q).

A. 0.15

B. 0.29

C. 0.39

D. 0.5

10. A patient with CKD who has a CL_{cr} of 50 mL/min (0.83 mL/s) is to receive a medication that has an f_e of 80%. The normal dose is 500 mg by mouth every 6 hours. Based on this information, calculate the most appropriate and practical adjusted dosage regimen for this patient.

    A. 250 mg every 6 hours

    B. 250 mg every 12 hours

    C. 500 mg every 6 hours

    D. 500 mg every 12 hours

11. Which of the following statements regarding the effects of dose and dosing interval adjustments in patients with impaired kidney function is CORRECT?

    A. If the dose is reduced while the dosing interval remains unchanged, then the peak will be higher and the trough lower.

    B. If the dose remains unchanged while the dosing interval is increased, then the peak and trough concentrations in patients with impaired kidney function will be similar to those in patients with normal kidney function.

    C. If the dose is reduced while the dosing interval remains unchanged, then the peak and trough concentrations in patients with impaired kidney function will be similar to those in patients with normal kidney function.

    D. If the dose remains unchanged while the dosing interval is increased, then the peak will be higher and the trough lower.

12. A 58-year-old man weighing 80 kg and with a measured CL_{cr} of 15 mL/min (0.25 mL/s) is to receive intravenous ciprofloxacin. The usual dose of ciprofloxacin is 500 mg every 12 hours for patients with normal kidney function. The relationship between ciprofloxacin clearance (CL_T) and kidney function is the following:

$CL_T = 2.83\,(CL_{cr}\text{ in mL/min}) + 363$CLT = 2.83 (CLcr in mL/min) + 363

    A. 250 mg every 12 hours

    B. 250 mg every 24 hours

    C. 500 mg every 24 hours

    D. 500 mg every 48 hours

Based on this information, calculate the most appropriate and practical adjusted dosage regimen for this patient. (Note: CL_{cr} results in mL/s must be divided by 0.0167 to use this equation.)

13. Which of the following statements regarding medication dialyzability by peritoneal dialysis is CORRECT?

    A. Medications that are unionized at physiologic pH will diffuse across the peritoneal membrane more slowly than ionized compounds.

    B. Blood flow and peritoneal membrane surface area are intrinsic properties of the peritoneal membrane that affect medication removal.

    C. Peritoneal dialysis is more effective than hemodialysis at removing medications.

D. Peritoneal medication clearance is higher for extensively protein bound medications

14. Which of the following medications is most likely to be removed by high flux hemodialysis?

A. Amlodipine (MW = 567 Da; V_D = 21.0 L/kg; plasma protein binding > 95%)

B. Atenolol (MW = 266 Da; V_D = 1.1 L/kg; plasma protein binding = 3%)

C. Clindamycin (MW= 476 Da; V_D = 0.8 L/kg; plasma protein binding= 94%)

D. Apixaban (MW = 460 Da; V_D = 0.3 L/kg; plasma protein binding = 87%)

15. Which of the following statements regarding medication removal by alternative hemodialysis modalities is CORRECT?

A. Medication removal during nocturnal hemodialysis is greater than during standard intermittent hemodialysis

B. Medication removal during nocturnal hemodialysis is negligible

C. Medication removal during short daily hemodialysis is less than standard intermittent hemodialysis

D. Medication removal during short daily hemodialysis is negligible

SELF-ASSESSMENT QUESTION-ANSWERS

1. **B.** Decreased GI motility can occur in CKD patients secondary to diabetic gastroparesis and may delay t_{max} and decrease C_{max}, thereby altering a medication's absorption. See the "Absorption and Bioavailability" section for more information.

2. **C.** Protein binding limits medication distribution, as only unbound or "free" medication is able to cross cellular membranes and distribute outside the vascular space. A decrease in plasma protein binging thus leads to increased distribution of medication. See the "Distribution" section for more information.

3. **D.** α1-Acid glycoprotein is major drug-binding plasma protein that primarily binds basic medications. Since it exhibits increased plasma concentrations in CKD, the unbound fraction of basic medications may be dramatically decreased leading to decreased V_D in CKD patients.

4. **A.** Renal clearance is a composite of all renal excretory functions, namely filtration, tubular secretion, and tubular reabsorption. Absorption is not involved in renal clearance. See the "Renal Clearance" section for more information.

5. **D.** Morphine undergoes hepatic metabolism into active metabolites, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), which readily cross the blood-brain barrier, bind to opiate receptors, and exert strong analgesic effects. In CKD patients, the clearance of M3G and M6G is decreased, potentially resulting in prolonged narcosis and respiratory depression. See the "Accumulation of Metabolites" section for more information.

6. **D.** The OATs are predominantly involved in basolateral uptake of medications into renal tubular cells from the plasma, thereby contributing to tubular secretion and net renal clearance of medications. Major nonrenal clearance pathways include oxidative metabolism by CYPs, conjugative metabolism by UGTs, and transport by OATPs.

7. **A.** Although it is infrequently updated, Aronoff's *Drug Prescribing in Renal Failure* exclusively focuses on medication dosing in patients with impaired kidney function and provides references to primary literature.

8. **B.** The method of Rowland and Tozer is useful for determining CL_T provided that f_e for subjects with normal kidney function is known. This approach assumes that the change in CL_T and k are proportional to eCL_{cr}, that kidney disease does not alter the medication's metabolism, that any metabolites that are formed are inactive and nontoxic, and that the medication obeys first-order (linear) one-compartment kinetic principles. See the "Medication Dosage Regimens for Non-Dialysis CKD Patients" section for more information.

9. **B.** Since the equation describing the relationship between kidney function and CL_T is not provided, the method of Rowland and Tozer can be used to determine the dosage adjustment factor (Q), as follows:

$$Q = 1 - [f_e(1 - \text{KF})]$$
$$\text{KF} = \text{CL}_{\text{CR (patient)}}/\text{CL}_{\text{CR (normal)}} = 20\,\text{mL/min} / 120\,\text{mL/min} = 0.167$$
$$Q = 1 - [0.85(1 - 0.167)] = 0.29$$

Q = 1 – [fe(1 – KF)]KF = CLCR (patient)/CLCR (normal) = 20 mL/min / 120 mL/min = 0.167Q = 1 – [0.85(1 – 0.167)] = 0.29

10. **D.** Since the equation describing the relationship between kidney function and CL_T is not provided, the method of Rowland and Tozer can be used to determine the dosage adjustment factor (Q), as follows:

$$Q = 1 - [f_e(1 - \text{KF})]$$
$$\text{KF} = \text{CL}_{\text{CR (patient)}}/\text{CL}_{\text{CR (normal)}} = 50\,\text{mL/min} / 120\,\text{mL/min} = 0.42$$
$$Q = 1 - [0.8\,(1 - 0.42)] = 0.54$$

Q = 1 – [fe(1 – KF)]KF = CLCR (patient)/CLCR (normal) = 50 mL/min / 120 mL/min = 0.42Q = 1 – [0.8 (1 – 0.42)]= 0.54

Increasing the dosing interval is the approach used most commonly to adjust dosage regimens in patients with impaired kidney function, so apply Q to the interval:

$$\tau_{\text{CKD}} = \tau_{\text{norm}}/Q$$
$$\tau_{\text{CKD}} = 6\,\text{hours}/0.54 = 11.1\,\text{hrs}$$

τCKD = τnorm/QτCKD = 6 hours/0.54 = 11.1 hrs

Use a practical interval, so recommend adjusted dosing regimen of 500 mg every 12 hours.

11. **B.** If the dose is decreased and the dosing interval remains unchanged, then the average steady-state concentration will be unchanged but the peaks will be lower and the troughs will be higher. Conversely, if the dosing interval is increased and the dose remains unchanged, then the average steady-state, peak, and trough concentrations in the patient with impaired kidney function will be similar to those in the patient with normal kidney function. See the "Designing Adjusted Renal Dosage Regimens" section for more information.

12. **C.** Since the equation describing the relationship between kidney function and CL_T is provided, it can be used to calculate the CL_T in the patient and to derive the dosage adjustment factor (Q), as follows:

$$CL_{T(\text{patient})} = 2.83(15\,\text{mL/min}) + 363 = 405\,\text{mL/min}$$
$$CL_{T(\text{normal})} = 2.83(120\,\text{mL/min}) + 363 = 703\,\text{mL/min}$$
$$Q = 405/703 = 0.57$$

CLT (patient) = 2.83(15 mL/min)+363 = 405 mL/minCLT (normal) = 2.83(120 mL/min)+ 363 = 703 mL/minQ = 405/703 = 0.57

Increasing the dosing interval is the approach used most commonly to adjust dosage regimens in patients with impaired kidney function, so apply Q to the interval:

$$\tau_{\text{CKD}} = \tau_{\text{norm}}/Q$$
$$\tau_{\text{CKD}} = 12\,\text{hours}/0.57 = 21\,\text{hrs}$$

τCKD=τnorm/QτCKD=12 hours/0.57 = 21 hrs

Use a practical interval, so recommend adjusted dosing regimen of 500 mg every 24 hours.

13. **B.** The intrinsic properties of the peritoneal membrane that affect medication removal include blood flow and peritoneal membrane surface area. There is an inverse relationship between peritoneal clearance of medications and protein binding. Medications that are ionized at physiologic pH will diffuse across the membrane more slowly than unionized compounds. In general, hemodialysis is more effective in removing medications than peritoneal dialysis.

14. **B.** Medication-related factors that affect dialyzability include the molecular weight, degree of protein binding, and V_D. High-flux hemodialysis membranes allow for the passage of medications that have a molecular weight up to 20,000 Da. Medications that are highly protein bound (i.e., >90%) are not well dialyzed. Finally, medications that are widely distributed, with V_D greater than 2 L/kg, are poorly removed by HD. See the "Principles of Hemodialytic Clearance of Medications" section for more information.

15. **A.** The blood and dialysate flow rates are typically slower for nocturnal hemodialysis than standard intermittent hemodialysis and thus clearance per unit of time will be less. However, since nocturnal hemodialysis is performed more frequently and for longer duration per session, it may result in an increase in medication removal compared to standard intermittent hemodialysis. See the "Alternative Hemodialysis Modalities" section for more information.