Principles of Kidney Pharmacotherapy for the Nephrologist: Core Curriculum 2021

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Medications are an important part of the management of patients with kidney disease. When used appropriately, pharmacotherapy can slow disease progression and reduce morbidity and mortality. Unfortunately, reduced kidney function can significantly alter the pharmacokinetics and pharmacodynamics of many medications, putting patients at risk for drug toxicity if modifications to therapy are not appropriately managed. Adding complexity to the appropriateness of medication and dosage selection is the difficulty in estimating kidney function and the discordance between the Cockcroft-Gault–derived dosing cut points in most medication package inserts and the estimations of glomerular filtration rate by newer and generally more accurate guideline-recommended equations. This installment of the AJKD Core Curriculum in Nephrology provides recent updates and practical considerations for designing optimal medication regimens. Given the prevalence of abnormal kidney function and its importance in medication selection and dose adjustment, additional focus and specific recommendations are provided for anticoagulant, anti-infective, analgesic, antidiabetic, and antihypertensive agents.

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Introduction

Patients with kidney disease carry an increased medication burden compared with patients with normal kidney function, with 80% of patients taking more than 5 medications per day. The prevalence of polypharmacy increases as chronic kidney disease (CKD) stage worsens and comorbidities increase. Dialysis patients have among the highest pill burdens of any disease state, with a median of 19 pills per day and with 25% of patients exceeding 25 pills per day. Elderly patients with CKD take a median of 9 medications daily and have additive alterations in pharmacokinetics and pharmacodynamics due to advanced age plus CKD. Their risk of an adverse drug event is 3 to 10 times higher than elderly patients without CKD. A study of 83,000 veterans with a creatinine clearance (CL_{cr}) of 15-49 mL/min reported inappropriate medication dosages or contraindications to therapy in 13% to 29% of patients, clearly demonstrating the importance of a systematic approach to reviewing and managing medications in patients with reduced kidney function.

Nephrologists are frequently faced with managing a variety of medication therapies that each have their own pharmacologic considerations for maximizing benefits and minimizing risks. Compounding this challenge is the paucity of pharmacokinetic or clinical data for many medications in patients with declining kidney function. The lack of therapeutic drug monitoring and frequent difficulties with medication adherence due to polypharmacy add significant complexity to the decision-making process. This installment of the AJKD Core Curriculum in Nephrology builds upon the basic pharmacologic principles laid out in the previous Core Curriculum installment from 2005 and highlights major concepts for the most common comorbidities and medications that require special consideration in patients with declining kidney function.

Additional Readings

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Basic Principles in Kidney Pharmacotherapy

Pharmacokinetics, pharmacodynamics, and pharmacogenomics provide the foundation for

drug selection and dosing considerations in patients with abnormal kidney function. In simple form, pharmacokinetics can be described as what the body does to a medication when it is administered. Absorption, distribution, protein binding, metabolism, and elimination are all pharmacokinetic parameters. Pharmacodynamics describe the action of the medication and resultant biochemical effects, which includes both desired and adverse effects. The pharmacodynamic effect of a drug can be determined by a concentration-time profile. Efficacy and safety parameters can be predicted by either maximum plasma concentration (C_{max}), area under the concentration time curve (AUC), or the amount of time spent above a concentration threshold. This principle is best illustrated with antibiotics (Fig 1). Pharmacogenomics provides a genetic basis for either pharmacokinetic or pharmacodynamic variability.

Abnormal kidney function results in pharmacokinetic alterations for many medications. Unfortunately, pharmacokinetic evaluations of medications in abnormal kidney function are commonly limited to small studies that may not be representative of all patients, and frequently data are missing for patients receiving dialysis. Therefore, a fundamental understanding of pharmacokinetic and pharmacodynamic principles is needed to design rational medication regimens for patients with abnormal kidney function.

Pharmacokinetic Considerations in CKD

Alterations in absorption, distribution, protein binding, metabolism, and elimination are all pharmacokinetic parameters that should be considered in patients with abnormal kidney function (Table 1). The gastrointestinal absorption of medications in most patients with kidney disease is similar to patients without kidney disease. The majority of studies that have demonstrated alterations in time to maximal concentration or measured maximal concentration have been driven by other conditions such as gastroparesis (eg, in diabetes), bowel edema, alterations in gastric pH (eg, use of H_2 receptor antagonists or proton-pump inhibitors), drug-drug interactions (eg, calcium-containing phosphate binders), or altered first-pass metabolism. For example, significant gastrointestinal edema may alter absorption of oral furosemide by more than 50%, especially in advanced CKD with concomitant cirrhosis or heart failure.

Increased volume of distribution (V_d) is observed for many medications due to increased plasma volume, increased total body water, or decreased protein binding. Hydrophilic medications will have increased V_d commensurate with increased volume in both patients with acute kidney injury (AKI) and CKD. This is best illustrated with aminoglycosides where the V_d increases by approximately 30% and has significant implications for first dose selection to achieve C_{max}/MIC (minimum inhibitory concentration) targets. Hypoalbuminemia results in decreased protein binding for many acidic medications (eg, penicillins, cephalosporins, furosemide, and phenytoin). Unbound drug distributes more easily into tissues, thereby increasing the V_d of the medication. Considering the equation $Concentration_{peak} = (Dose \times Bioavailability)/V_d$, increased V_d portends a need for an increased first dose to achieve the desired plasma concentration. A notable exception to this concept is digoxin, which has a decreased

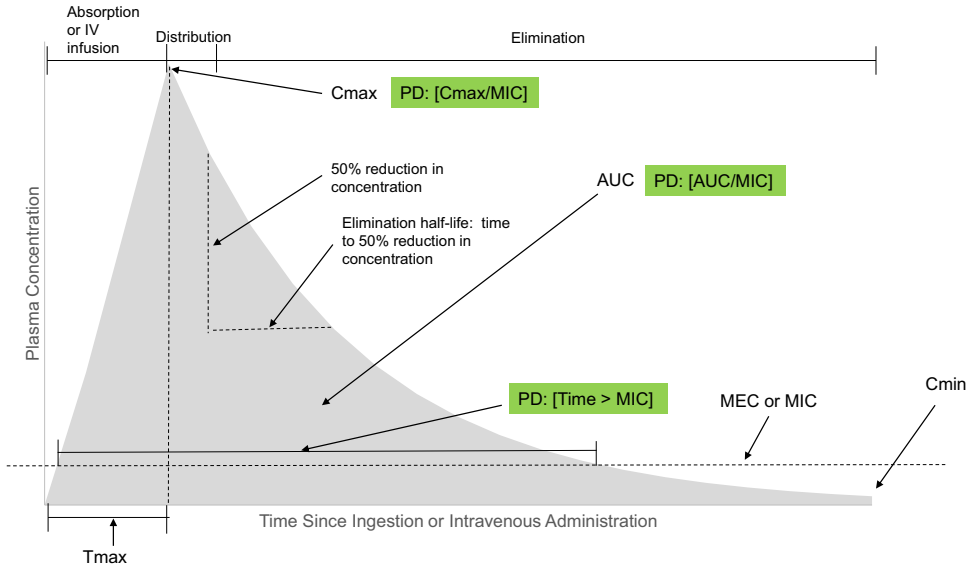

Figure 1. Pharmacokinetic phases and pharmacodynamic parameters. Typical plasma or serum concentration-time curve for most medications. Pharmacodynamic parameters are a relationship between the absolute concentration compared to the minimum effective concentration (C_{max}/MIC), total drug exposure over the dosing interval (AUC/MIC), or the time the concentration spends above the minimum inhibitory concentration (T > MIC). Abbreviations: AUC, area under the concentration time curve; C_{max}, maximal concentration (peak); C_{min}, minimum concentration (trough); IV, intravenous; MEC, minimum effective concentration; MIC, minimum inhibitory concentration; PD, pharmacodynamic; T_{max}, time to maximal concentration.

Table 1. Pharmacokinetic Considerations With Reduced Kidney Function

Pharmacokinetic Parameter	Usual Changes	Implications
Absorption	Mostly unchanged	• Oral dosage forms: Gastroparesis in patients with diabetes, bowel edema, or interactions with phosphate binders (eg, calcium + tetracyclines or fluoroquinolones) may reduce absorption. Decreased first-pass metabolism may increase bioavailability of certain medications (eg, β-blockers, propoxyphene). • Subcutaneous administration: Significant subcutaneous edema may reduce or slow absorption (eg, enoxaparin, insulin). • Intravenous administration: unaffected.
Distribution	Increased Hydrophilic > lipophilic	• Hydrophilic medications (eg, aminoglycosides, vancomycin, daptomycin) distribution will increase with increased total body water. First dose may need to be increased. • Hypoalbuminemia or alterations in plasma protein or tissue binding due to uremia will significantly increase volume of distribution. First dose may need to be increased.
Protein binding	Decreased	• Protein binding is decreased due to hypoalbuminemia and alterations in protein binding sites or binding competition with other medications or accumulated uremic albumin-bound retention solutes. The resulting increased free fraction of the drug can increase the risk of drug adverse events and may require a reduction in dose.
Metabolism	Decreased	• Reduced metabolism is dependent on degree of reduction in kidney function and on resultant effect on hepatic enzymes. Reduction in dose of narrow therapeutic index medications may be needed.
Elimination	Decreased	• Kidney elimination significantly reduced for medications where the active compound is >25% cleared by the kidneys. Reduced maintenance dosage is warranted. Reduction in dose and/or frequency is chosen based upon pharmacodynamic properties and convenience.

V_d due to reduced tissue binding in patients with kidney failure. Binding to the plasma protein α-1-acid glycoprotein (AAG), which is primarily responsible for the binding of basic medications, appears less affected and may even be increased due to its acute phase reactant nature in patients with kidney disease.

Protein binding alterations due to kidney disease are most notable with albumin-bound medications. Increased unbound concentration of medications may significantly increase exposure and adverse events if hepatic extraction or other methods of elimination do not more effectively remove the unbound fraction. This is best demonstrated with narrow therapeutic index drugs like phenytoin. Patients with AKI or CKD may have therapeutic free phenytoin concentrations even with subtherapeutic total phenytoin concentrations due to the increased free fraction. Such patients may also have toxic free phenytoin concentration with normal total phenytoin concentrations. In these situations, it is best to measure free and total plasma concentrations of the medications when access to a laboratory that can perform these measurements is available. Although they are less accurate and vary based upon severity of illness, estimation equations can also be used, such as $\text{Concentration}_{\text{normal binding}} = \text{Concentration}_{\text{reported}} / [0.9 \times (0.48 \text{ if dialysis}) \times \text{Patient's albumin}/4.4] + 0.1$.

Alteration in medication clearance is probably the most obvious pharmacokinetic parameter driving the need for alterations in drug maintenance dosing. Reductions in medication clearance increase a drug's half-life, time to steady state, and risk of drug accumulation over time. Kidney clearance of medications that are predominantly filtered or secreted into the tubules are most affected by decreased kidney function. The impact of drug elimination will depend on the proportion of unchanged drug elimination by the kidneys and the impact of glomerular filtration versus tubular secretion, which can decline asynchronously. However, commonly overlooked is the potential impact of kidney disease on the nonkidney clearance of highly metabolized medications. In addition to reduced kidney clearance, a reduction in hepatic enzyme activity (~5%-50% depending on the enzyme) has been observed in patients with CKD. Accumulation of uremic toxins can result in inhibition of intestinal, kidney, and hepatic drug transporters impacting medication efflux (eg, P-glycoprotein) or uptake (eg, organic anion transporters), causing rate limitations in metabolism and elimination of many medications. In general, reductions in elimination result in the need to reduce the total daily dose (by adjusting either dose and/or frequency).

Although we most commonly consider the pharmacokinetics of the parent drug, for certain medications we also should consider metabolites and stabilizing excipients/diluents within drug preparations (eg, cyclodextrin in intravenous voriconazole or posaconazole; propylene glycol in intravenous lorazepam). For example, the pharmacokinetics of meperidine are mostly unaltered in patients with kidney disease. However, the active metabolite, normeperidine, accumulates in patients with reduced kidney function and can result in seizures. Other examples include procainamide, clofibrate, allopurinol, nitrofurantoin, and certain sulfa antibiotics.

Pharmacodynamic Considerations in CKD

Most alterations in drug effect are due to pharmacokinetic changes rather than true pharmacodynamics response modification resulting from altered receptor effects in patients due to kidney disease. The most common example of altered drug response has been noted with loop diuretics, where increased tubular concentrations are needed to produce the desired diuretic effect as kidney disease worsens.

Due to the paucity of data clearly demonstrating increased or decreased sensitivity to medications in kidney disease, pharmacodynamics are primarily used to design an appropriate strategy for adjusting drug dosing. Medications are frequently placed into "concentration-dependent" or "time-dependent" categories. Concentration-dependent medications are those where the resultant effects are best predicted by the highest concentration achieved (eg, peak concentration). Time-dependent medications are those that require a concentration to stay above a threshold for a period of time. Using these principles, concentration-dependent medications are usually administered in larger doses less frequently whereas time-dependent medications are administered either in more frequent smaller doses or by continuous infusion.

Pharmacogenomic Principles in Kidney Pharmacology

Pharmacogenomics is a growing field with clinical implications for medication selection and drug dosing. Specific genetic information gathered from a patient can help the nephrologist determine whether or not to choose a specific medication (eg, azathioprine in altered thiopurine methyltransferase function or clopidogrel in patients with reduced CYP2C19 function) or whether genetics would predict an alteration in pharmacokinetics leading to significant dose adjustments (eg, tacrolimus, voriconazole, or warfarin).

In addition to altered pharmacokinetics, pharmacogenomics can help predict unusual but devastating reactions. An *HLA-B* (major histocompatibility complex, class I, B) gene may predict the occurrence of Stevens-Johnson syndrome and toxic epidermal necrolysis with allopurinol. Evaluation of glucose 6-phosphate dehydrogenase (G6PD) deficiency has implications for many prophylactic or treatment options for opportunistic infections in kidney transplant patients (eg, primaquine or dapsone). Up-to-date pharmacogenomic implementation recommendations can be found on the Clinical Pharmacogenetics Implementation Consortium (CPIC) website (www.cpicpgx.org).

Basic Principles Regarding Dosing Regimens in Patients With CKD

The first considerations surrounding designing a drug dosing regimen incorporate the medication's pharmacologic profile and the ascertainment of potential benefits and risks for the patient. In general, dose adjustments are less important if the drug has a wide therapeutic index (eg, most β-lactam antibiotics) or the duration of therapy is short (one-time doses or less than 3 days). Most narrow therapeutic index medications have therapeutic drug monitoring available, and the resultant plasma concentrations should be used to design patient-specific dosing regimens when the concentrations become available (Box 1).

Once an appropriate medication is chosen, an empirical dosing regimen needs to be designed. For most medications, the first dose, or loading dose, will be the same or higher (due to increased V_d, as discussed earlier) compared with patients with normal kidney function. This is because the concentration achieved on the first dose is dependent on the V_d rather than drug elimination. Figure 2 illustrates the importance of a loading dose for achieving target concentrations when the plasma half-life is prolonged due to decreased kidney clearance.

Subsequent doses after the initial dose, commonly referred to as the maintenance dose, require more careful consideration in patients with abnormal kidney function. Depending on the pharmacodynamics of the medication, changing the interval, dose, or both can be the preferred choice. Regardless of the strategy, it is important to understand that a drug's half-life determines the time to achieve steady-state concentrations (97% of steady-state is achieved after 5 half-lives). Giving bigger doses less frequently results in higher peak concentrations and lower trough concentrations (Fig 2). This can be advantageous for medications like aminoglycosides or daptomycin where high peak concentrations are associated with

Box 1. Dosing Adjustment Considerations With Reduced Kidney Function

Wide Therapeutic Index Medication

No adjustment needed

- Short duration of therapy (<3-7 d), such as fluconazole for vulvovaginal candidiasis
- Low or prophylactic dosing, such as trimethoprim/sulfamethoxazole PJP prophylaxis
- AKI likely reversible (due to decreased perfusion), such as antibiotics for septic shock

Adjustment needed

- Accumulation associated with ADR, such as cefepime encephalopathy

Narrow Therapeutic Index Medication

No adjustment needed

- Patient-specific first dose or loading dose, such as warfarin, theophylline, phenobarbital

Adjustment needed

- All maintenance dosages, such as all renally eliminated medications
- Dosing by therapeutic drug monitoring, such as aminoglycosides, phenytoin, lithium, digoxin

Abbreviations: ADR, adverse drug reaction; AKI, acute kidney injury; PJP, Pneumocystis jiroveci pneumonia.

increased efficacy and lower trough concentrations reduce the risk of toxicity. The use of smaller doses given more frequently, including extended or continuous infusions, can optimize drug exposure over time and minimize concentrations that are too high or low. This approach can be optimal for β-lactam antibiotics, antidiabetic agents, antihypertensives, analgesics, and others.

Dosing Adjustment in Kidney Failure With Replacement Therapy

Kidney replacement therapy (KRT) adds a layer of complexity to drug dosing because the clearance of dialyzable medications differs significantly during the time on dialysis compared with when the patient is not undergoing dialysis, and drug clearance depends on any residual kidney function. Drugs that are hydrophilic, uncharged, and have small V_d and low protein binding are most likely to be removed by extracorporeal dialysis.

In general, peritoneal dialysis is the least effective and intermittent hemodialysis (HD) is the most effective at rapidly removing medications. However, due to the short duration of intermittent HD and typical use of 3 times per week therapy, continuous kidney replacement therapy (CKRT) or prolonged intermittent kidney replacement kidney replacement therapy (PIKRT) modalities are the most effective at removing medications over a week. CKRT also allows for drug redistribution over time from the tissues to the plasma. It is important to note that dosing regimens recommended for intermittent HD will result in significant underdosing of most medications in patients on CKRT. In the absence of pharmacokinetic data from published studies using similar equipment and filters, incorporation of the CKRT flow rates and the individual drug's sieving coefficient is important for estimating drug dosing according to the CL_{cr} cut points found in the medication's package insert (CL_{CVVH} = UFR × Sieving coefficient, where CVVH is continuous venovenous hemofiltration and UFR is the ultrafiltration rate).

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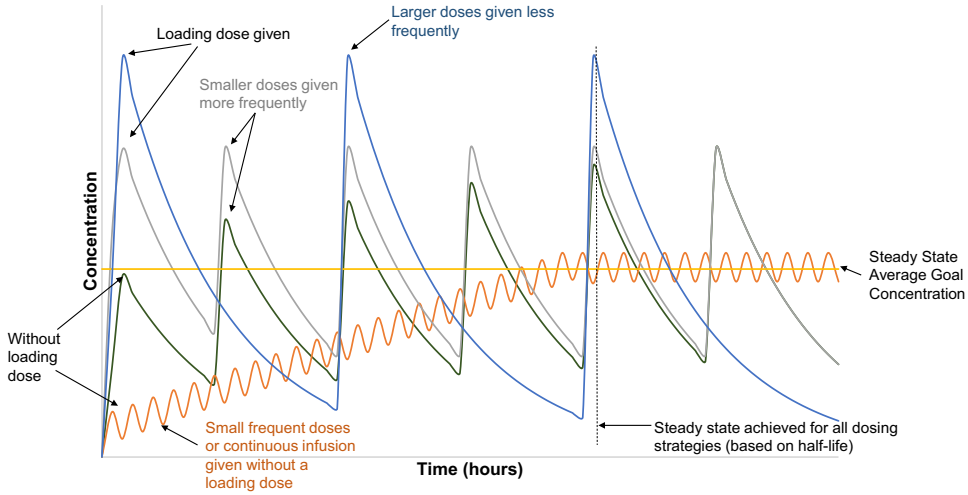

Figure 2. Examples of different dosing strategies and resultant concentrations over time. Patients with reduced kidney function frequently have reduced drug clearance and increased elimination half-life. The blue and grey dosing scenarios show the importance of a loading dose for achieving goal concentrations earlier in therapy. Giving larger doses less frequently can be advantageous for concentration-dependent medications and those with toxicities dependent on trough concentrations (eg, aminoglycosides). Giving smaller doses more frequently or continuous infusions (with a loading dose) can be advantageous for medications that have more time-dependent effects (eg, β-lactam antibiotics) or in those where peak concentrations are associated with toxicity (eg, 5-flucytosine).

Kidney Function Estimates for Drug Dosing

Case 1: *An 82-year-old woman is admitted to the hospital with a urinary tract infection and failure to thrive. She weighs 120 lb and is 5 ft, 5 in tall. Her serum creatinine concentration (Scr) today is 1.4 mg/dL and is stable. She has a history of hypertension, type 2 diabetes, hypothyroidism, and atrial fibrillation.*

Question 1: Which of the following statements is correct regarding drug dosage adjustments in this patient?

a) Should be based on her estimated glomerular filtration rate (eGFR), which is 35 mL/min/1.73 m^2
b) Should be based on her individualized eGFR, which is 32 mL/min
c) Should be based on her estimated CL_{cr}, which is 27 mL/min
d) The best kidney function estimate to use depends on the drug and what is recommended in the approved package labeling.

For the answer to the question, see the following text.

Patients with CKD experience a variety of complications and comorbidities that lead to a high medication burden. Given that over half of all medications used in practice undergo extensive kidney elimination, patients with CKD are most vulnerable to potential drug accumulation and toxicity if drug doses are not adjusted appropriately. Therefore, accurate measurement of kidney function is important for appropriate drug dosing in these patients.

The Modification of Diet in Renal Disease (MDRD) Study equation and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation use Scr, age, sex, and race to predict measured glomerular filtration rate (GFR). They are adjusted for a normal body surface area (BSA) and expressed as mL/min/1.73 m^2. The National Kidney Foundation (NKF) recommends these equations be used for staging of CKD, with the CKD-EPI creatinine equation as the preferred option. Most institutions automatically report the eGFR (in mL/min/1.73 m^2) in the laboratory section of the patient's electronic health record.

More recently, the use of race in these equations has become controversial, with many institutions removing race from the equations. Race was originally incorporated in these equations based on the observation that measured GFR was higher in Black individuals compared to non-Black individuals. However, race is not an objective parameter, and it does not adequately capture the diversity within a population. There are concerns that using race in these equations may impact equity for Black patients with regard to eligibility for specialist care and kidney transplantation. The NKF and the American Society of Nephrology (ASN) have formed a joint task force to review the use of race in estimating GFR. This task force will look for a better way other than race to ensure unbiased estimates of GFR.

The Cockcroft-Gault (CG) equation is the most common equation used to calculate estimated creatinine clearance (eCL_{cr}). This equation adjusts for age, sex, and weight (in kilograms), and is expressed in milliliters per minute. This equation is also the most common method recommended for estimating kidney function for dosage adjustments in US Food and Drug Administration (FDA) package labeling. It is for this reason that most pharmacists advocate using various forms of the CG equation instead of the newer equations to determine drug dosing adjustments in patients with reduced kidney function.

A major dilemma with using the CG equation is that its development occurred before creatinine standardization, and studies have shown the CG equation results in overestimation of CL_{cr} when used with current standardized assays. Based on the limitations of the CG equation, the NKF recommends that individualized MDRD Study or CKD-EPI creatinine equations, using the patient's BSA to remove the normalization, be used for drug dosing decisions. Using a single kidney function estimate for staging CKD and for most dosage adjustments is supported by KDIGO, and this could improve the quality of patient care by reducing confusion and thereby increasing consistency among clinicians and institutions.

The FDA published a draft guidance for industry (*Pharmacokinetics in Patients with Impaired Renal Function—Study Design, Data Analysis, and Impact on Dosing*) in September 2020. In the guidance they recommend the use of eGFR to determine kidney function in pharmacokinetic studies and the use of individualized (non–BSA-standardized) eGFR for drug dosing. However, this guidance also states that "any contemporary, widely accepted, and clinically applicable estimating equation for the population being studied is considered reasonable to assess renal function in PK studies."

The variety of equations available to estimate kidney function has created confusion for clinicians as to the best approach, and there are limitations and benefits to using each of the estimation equations. Using the kidney function estimation method recommended for drug dosage adjustments in the approved package labeling is what is supported by KDIGO. Therefore, the correct answer to question 1 is (d). This can be challenging because for some drugs the doses are adjusted based on the original CL_{cr} equation whereas some resources might state to use CL_{cr} but do not specify which equation, and some adjustments use eGFR (mL/min/1.73 m^2). Another option that may be valuable for higher risk populations (those aged > 75 years, representing extremes in body weight, receiving high-risk medications, or receiving medications for high-risk conditions) is to consider the results of a couple of different kidney function estimation methods and pick the estimate that optimizes the dosage adjustment and balances the potential risks and benefits. Further discussion of

kidney function estimate limitations and alternatives to Scr can be found in Item S1.

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Select Medications That Require Special Consideration in Patients With Declining Kidney Function

Anticoagulants

Case 2: *A 72-year-old man presents to the hospital with rapid ventricular response (heart rate 130-139 beats per minute), and new onset nonvalvular atrial fibrillation is diagnosed. The patient's medical history is significant for type 2 diabetes, hypertension, dyslipidemia, and CKD GFR category 5 (CKD G5; based on an eGFR of 12 mL/min/1.73 m^2). The estimated CL_{cr} (using the CG formula, a weight of 70 kg, and a Scr of 4.60 mg/dL) is 14 mL/min. The patient has a CHA_2DS_2-VASC score of 3, and anticoagulation is being considered to reduce his risk for future stroke.*

Question 2: Based on their different pharmacokinetic dependence on the kidneys for elimination, which of the following direct-acting oral anticoagulants would be best to recommend for this patient?

a) Dabigatran at 75 mg orally, twice daily
b) Edoxaban at 30 mg orally, once daily
c) Apixaban at 5 mg orally, twice daily
d) Rivaroxaban at 20 mg orally, daily with dinner

For the answer to the question, see the following text.

A plethora of information has been published recently on the topic of anticoagulation in patients with CKD. Patients with CKD are at high risk for nonvalvular atrial fibrillation (NVAF) and are frequently at higher risk for venous thromboembolism (VTE) due to underlying conditions and CKD, which increases thrombotic risk. CKD is an independent risk factor for stroke, and stroke risk has been shown to increase by 7% for every 10 mL/min/1.73 m^2 decrease in GFR. Despite this increased risk, patients with severely decreased GFR have been universally excluded from trials evaluating the efficacy and safety of warfarin and direct-acting oral anticoagulants (DOACs).

All DOACS depend to a certain extent on kidney function for elimination, with dabigatran (80%) and edoxaban (50%) being most dependent followed by rivaroxaban (36%) and apixaban (25%). Careful consideration of DOAC pharmacologic properties reveals an opportunity for use depending on the agent, indication, and severity of GFR decrease (Table 2). The 2019 AHA/ACC/HRS guideline recommendations for anticoagulation in patients with CKD and atrial fibrillation are summarized in Table S1. They suggest treating patients with NVAF, elevated CHA_2DS_2-VASC scores, and CKD G3-G4 with reduced doses of a DOAC. In patients with CKD G5 or on dialysis, they recommend warfarin or apixaban.

Based on the limited available data, the oral anticoagulant of choice in patients with CKD G4-G5 should be apixaban, which has demonstrated similar efficacy and a better safety profile in this population when compared with warfarin and other DOACs. Although bleeding rates with apixaban are lower than with other oral anticoagulants, it is important to keep in mind that the rates are still higher than those seen in patients with normal kidney function. Warfarin therapy is associated with higher rates of major bleeding (particularly intracranial hemorrhage) and difficulty maintaining the international normalized ratio (INR) in the therapeutic range, and it has an added theoretical risk for vascular calcification and anticoagulant-associated nephropathy, which makes its use concerning in CKD G4-G5.

If apixaban is used, per package labeling, the dosage should be reduced from 5 mg twice daily to 2.5 mg twice daily when 2 of the following are present: Scr >1.5 mg/dL, weight < 60 kg, age >80 years. Using these dosing recommendations in patients with CKD G4-G5 and those on dialysis is controversial, and they are based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data that are conflicting. Mavrakanas et al found that the standard dose of apixaban (5 mg orally twice daily) for 8 days in patients on HD resulted in drug levels that were supratherapeutic. However, single-dose pharmacokinetic studies in patients on dialysis have suggested that apixaban can be used without dose modification; the study by Siontis et al demonstrated improved outcomes with the standard dose regimen. The correct answer to question 2 is therefore (c).

Of the injectable anticoagulants, unfractionated heparin is the safest to use in patients with CKD G4-G5. Unfractionated heparin is primarily metabolized in the liver and endothelium and does not require dosage adjustment with decreased kidney function. Its anticoagulant effects can also be completely reversed using protamine sulfate. The low-molecular-weight heparin (LMWH) enoxaparin is primarily eliminated by the kidneys and should be adjusted when CL_{cr} falls below 30 mL/min. The terminal half-life

Table 2. Dosing Recommendations for Oral Anticoagulants

Anticoagulation	Dosing NVAF	Dosing VTE Treatment	Other
Warfarin	Patients with CKD may require doses that are 20% less than patients with normal kidney function		• The worse the kidney function, the lower the TTR • Not preferred in severe CKD due to increased risk for vascular calcifications
DOACs			
Apixaban	5 mg 2×/d or 2.5 mg 2×/d if any 2 of the following present: Scr ≥ 1.5 mg/dL, age ≥ 80 years, weight ≤ 60 kg	10 mg 2×/d for 7 days, followed by 5 mg 2×/d; no dosage adjustment recommended	• No recommended dosage adjustment in patients on dialysis based on PK/PD data • Preferred DOAC in CKD G4-G5 • 14% dialyzable
Rivaroxaban	CL_{cr} ≥ 50 mL/min: 20 mg 1×/d with food CL_{cr} < 50 mL/min: 15 mg 1×/d with food CL_{cr} < 15 mL/min: NR	CL_{cr} ≥ 15 mL/min: 15 mg 2×/d with food for 21 days, then 20 mg 1×/d with food CL_{cr} < 15 mL/min: NR	• Minimally (<10%) dialyzable • No clinical data in dialysis patients; appropriate dose unknown
Edoxaban	CL_{cr} > 50-≤95 mL/min: 60 mg 1×/d CL_{cr} 15-50 mL/min: 30 mg 1×/d CL_{cr} < 15 mL/min: NR	CL_{cr} > 50 mL/min: 60 mg 1×/d CL_{cr} 30-50 mL/min: 30 mg 1×/d if body weight ≤ 60 kg, or therapy with verapamil, dronedarone, or quinidine	• In part (~25%) dialyzable • For VTE, start after 5-10 days of initial therapy with a parenteral anticoagulant
Dabigatran	CL_{cr} > 30 mL/min: 150 mg 2×/d CL_{cr} 15-30 mL/min: 75 mg 2×/d CL_{cr} < 15 mL/min: NR	CL_{cr} > 30 mL/min: 150 mg 2×/d CL_{cr} ≤ 30 mL/min: NR	• 40%-50% dialyzable • For VTE, start after 5-10 days of initial therapy with a parenteral anticoagulant

All drugs listed above are given orally. Abbreviations: CL_{cr}, creatinine clearance; CKD, chronic kidney disease; DOACs, direct-acting oral anticoagulants; NVAF, nonvalvular atrial fibrillation; NR, not recommended; PD, pharmacodynamics; PK, pharmacokinetics; Scr, serum creatinine concentration; TTR, time within therapeutic range; VTE, venous thromboembolism.

of the LMWH dalteparin is also increased in patients with severely reduced kidney function, but no dosage adjustments are recommended. If LMWHs are to be used in CKD G5, anti–factor Xa level monitoring should be considered. Fondaparinux is an injectable factor Xa inhibitor. It undergoes extensive kidney elimination and is not recommended for use in patients with a CL_{cr} < 30 mL/min. Bivalirudin and argatroban are parenteral direct thrombin inhibitors that are used in the management of acute coronary syndrome or in patients with heparin-induced thrombocytopenia (HIT) or a history of HIT. Bivalirudin is primarily cleared by the kidneys and requires dosage adjustment at a CL_{cr} < 30 mL/min. Argatroban is hepatically cleared and is preferred in CKD G4-G5. While both argatroban and bivalirudin can increase the prothrombin time and INR in a dose-dependent fashion, argatroban's effects are more pronounced, which can make titration of warfarin therapy very challenging. Table 3 summarizes the dosing recommendations for injectable anticoagulants for patients with decreased kidney function.

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Table 3. Dosing Recommendations for Injectable Anticoagulants

Anticoagulation	Dosing	Other
Unfractionated heparin	No dosage adjustment needed	Antidote (protamine)
Direct thrombin inhibitors		
Bivalirudin	CL_{cr} < 30 mL/min: reduce IV infusion rate to 1 mg/kg/h HD: reduce IV infusion rate to 0.25 mg/kg/h	
Argatroban	No dosage adjustment needed	Up to 2-fold "false" increase in PT/INR
Low-molecular-weight heparins		
Enoxaparin	CL_{cr} ≥ 30 mL/min: 1 mg/kg SC 2×/d CL_{cr} < 30 mL/min: 1 mg/kg SC 1×/d	Consider monitoring anti-Xa levels in patients with a CL_{cr} < 15 mL/min
Dalteparin	CL_{cr} ≥ 30 mL/min: 200 IU/kg SC 1×/d for 30 d then 150 IU/kg SC 1×/d CL_{cr} < 30 mL/min: no recommendation	
Factor Xa inhibitor: fondaparinux	CL_{cr} ≥ 30 mL/min: 5 mg (body weight < 50 kg), 7.5 mg (50-100 kg) or 10 mg (>100 kg) by SC injection 1×/d CL_{cr} < 30 mL/min: NR	

Abbreviations: CL_{cr}, creatinine clearance; HD, hemodialysis; INR, international normalized ratio; IV, intravenous; NR, not recommended; PT, prothrombin time; SC, subcutaneous.

➢ Wanner C, Herzog CA, Turakhia MP; Conference Steering Committee. Chronic kidney disease and arrhythmias: highlights from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int.* 2018;94(2):231-234.

Antidiabetic Agents

Dosing adjustments for common antidiabetic agents in kidney dysfunction are summarized in Table 4. Further detail is provided in Item S2 and Tables S2 and S3; in addition, use of antidiabetic agents will be the focus of an upcoming Core Curriculum installment on management of diabetes in patients with CKD.

Antihypertensives

Considerations in the use of antihypertensives in patients with declining kidney function are covered in Item S3. Please also refer to "Hypertension in CKD: Core Curriculum 2019" (https://doi.org/10.1053/j.ajkd.2018.12.044).

Analgesics

Case 3: *A 67-year-old woman presents with worsening diabetic neuropathic pain. She has a past medical history significant for CKD G4, type 2 diabetes, hypertension, and depression. Her health care provider would like to start her on duloxetine at 30 mg orally daily to help with both her depression and neuropathic pain. Her most recent eGFR and eCL_{cr} are 25 mL/min/1.73 m² and 27 mL/min, respectively.*

Question 3: Which of the following is true regarding the use of duloxetine in this patient?

a) Duloxetine is contraindicated in patients with a CL_{cr} < 30 mL/min due to an increase in severe adverse effects.
b) Duloxetine is recommended in Europe and Canada at initial starting doses of 30-40 mg orally daily in patients with a GFR < 30 mL/min/1.73 m².
c) Duloxetine dose needs to be reduced to 30 mg orally daily in patients with a CL_{cr} < 30 mL/min.

Case 4: *A 59-year-old man is admitted with pancreatitis due to severe hypertriglyceridemia. His past medical history is significant for CKD G4, uncontrolled type 2 diabetes, hypertension, and dyslipidemia. Because the patient can take nothing by mouth, the team would like to start him on an intravenous (IV) opioid for pain.*

Question 4: Which of the following statements is true regarding opioid use in patients with CKD?

a) Morphine IV should be avoided if possible due to accumulation of metabolites that are excreted by the kidney.
b) Hydromorphone IV should be avoided due to the accumulation of metabolites that are excreted by the kidney.
c) Fentanyl IV should be avoided due to the accumulation of metabolites that are excreted by the kidney.
d) Although IV formulations of opioids should be avoided in patients with CKD, oral formulations are safe.

For the answers to these questions, see the following text.

According to the 2018 Annual Data Report from the US Renal Data System, the overall proportion of CKD patients in the United States using opioids in 2016 was 43.8%. Opioid use has been associated with altered mental status, falls, and fractures in severe CKD. Limiting opioid use and maximizing non-opioid alternatives as well as non-pharmacologic therapy such as acupuncture, exercises, and cognitive behavioral therapy is important in this population, who are at higher risk for adverse effects. When pharmacologic therapy is needed, choosing an appropriate agent can be challenging in this population due to comorbidities that accompany kidney disease and the impact of reduced kidney function on the normal pharmacokinetics of analgesic medications. If opioid use cannot be avoided, it is essential to use the lowest dose and for the

Table 4. Dosage Adjustment Recommendations: Antidiabetic Agents

Drug	Recommended Adjustments
Insulin	• Reduce dose by ~25% when the CL_{cr} is 10-50 mL/min • Reduce dose by up to 50% when the CL_{cr} is <10 mL/min
SGLT2 inhibitors	
Empagliflozin	• Not recommended for use in patients with an eGFR < 30 mL/min/1.73 m^2
Canagliflozin	• Use maximum dosage of 100 mg orally daily if eGFR 30-60 mL/min/1.73 m^2 • eGFR < 30 mL/min/1.73 m^2 with albuminuria >300 mg/d: Initiation is not recommended but may continue at 100 mg once daily • Contraindicated in patients on dialysis
Dapagliflozin	• Not recommended for initiation of treatment in eGFR < 25 mL/min/1.73 m^2 • Contraindicated in patients on dialysis
Biguanide	
Metformin	• If eGFR 30-44 mL/min/1.73 m^2, initiate therapy at half the usual dose (eg, 250 mg/d) and titrate to a maximum of 1 g/d only if there is no active kidney disease and/or conditions that predispose to hypoperfusion and hypoxemia (eg, acute heart failure, dehydration) • If eGFR falls to 30-44 mL/min/1.73 m^2 during therapy, consider benefits/risks of continuing therapy; if continuing, reduce dosage by 50% to a maximum of 1 g/d • Use contraindicated at eGFR < 30 mL/min/1.73 m^2
GLP-1 agonists	
Liraglutide	• No dosage adjusted recommended
Semaglutide	• No dosage adjusted recommended
Albiglutide	• No dosage adjusted recommended
Dulaglutide	• No dosage adjusted recommended
Exenatide	• Immediate release: Use not recommended at CL_{cr} < 30 mL/min • Extended release: Use not recommended at eGFR < 45 mL/min/1.73 m^2
Lixisenatide	• Use is not recommended (has not been studied) at eGFR < 15 mL/min/1.73 m^2
DDP-4 inhibitors	
Alogliptin	• CL_{cr} 30-59 mL/min: 12.5 mg orally daily • CL_{cr} 15 to 29 mL/min and HD: 6.25 mg orally daily • No data for PD
Saxagliptin	• eGFR < 45 mL/min/1.73 m^2 and HD: 2.5 mg orally daily • No data for PD
Sitagliptin	• eGFR 30-44 mL/min/1.73 m^2: 50 mg orally daily • eGFR < 30 mL/min/1.73 m^2 and HD/PD: 25 mg orally daily
Linagliptin	• No dosage adjustment
Sulfonlyureas	
Glimepiride	• No dosage adjustment needed; conservative starting doses recommended • Consider alternative if eGFR < 15 mL/min/1.73 m^2
Glipizide	• No dosage adjustment needed; conservative starting doses recommended • Avoid use if possible at an eGFR <10 mL/min/1.73 m^2
Glyburide	• CL_{cr} < 50 mL/min: Avoid use due to increased risk for hypoglycemia
Meglitinides	
Repaglinide	• CL_{cr} 20-40 mL/min: Initiate at 0.5 mg with meals • CL_{cr} < 20 mL/min and HD: No recommendations (has not been studied)
Nateglinide	• eGFR < 30 mL/min/1.73 m^2: conservative starting dose of 60 mg 3×/d with meals • eGFR <15 mL/min/1.73 m^2: Use with caution
Thiazolidinedione	
Pioglitazone	• No dosage adjustment

Abbreviations: CL_{cr}, creatinine clearance; DDP-4, dipeptidyl peptidase 4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide 1; HD, hemodialysis; PD, peritoneal dialysis; SGLT2, sodium glucose co-transporter 2.

shortest duration possible and to choose the safest opioid based on known pharmacokinetic characteristics of the drugs.

Non-opioid alternatives for chronic pain include acetaminophen, capsaicin topical cream, topical nonsteroidal anti-inflammatory drugs (NSAIDs), lidocaine topical patch, gabapentin and pregabalin, tricyclic antidepressants, and serotonin and norepinephrine reuptake inhibitors (Table 5). Systemic NSAIDs are not preferred alternatives for chronic pain in CKD due to their many risks. NSAIDS can inhibit platelet function and irritate the gastric mucosa, which can increase the risk for bleeding, especially in patients with uremia. They have nephrotoxic effects including a decrease in GFR through a reduction in prostaglandin-dependent renal blood flow, and they are associated with interstitial nephritis and nephrotic syndrome. They can also worsen hypertension, edema, and hyperkalemia. NSAIDs are contraindicated in patients with CKD G5. They should only be

used on a case-by-case basis with close monitoring in patients with CKD G4. NSAIDs can be safely used in CKD G1-G3 in select patients with appropriate monitoring. Short-term use, lower doses, and as-needed regimens are preferred when possible. Meloxicam and naproxen have long half-lives and are not a good choice in patients with CKD. Although COX-2 inhibitors have a lower risk for bleeding, they are still associated with adverse effects on kidney function, blood pressure, and edema, and they should be avoided in patients with CKD who are at risk for coronary artery disease.

Acetaminophen is the non-opioid agent of choice for treating mild to moderate pain in patients with CKD. No dosage adjustments are needed, but limiting use to ≤4 g daily is recommended. Tricyclic antidepressants do not require dosage adjustments in patients with CKD. However, they can increase the QT interval and are associated with significant anticholinergic side effects (eg, orthostasis, sedation, constipation, urinary retention, confusion, and dry mouth), which can be problematic, especially for older patients with CKD. Desipramine and nortriptyline have fewer anticholinergic effects and would be a safer option at lower doses if needed.

Both gabapentin and pregabalin require significant dosage adjustments to reduce the risk for accumulation. In a large cohort study of patients on HD, both drugs were associated with a risk for altered mental status, falls, and fractures. In some cases, this risk was present even at doses lower than that recommended by guidelines. Gabapentin and pregabalin should be used with caution in patients on HD. Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor that can be used for depression, generalized anxiety disorder, and neuropathic pain. Unfortunately, this therapy is frequently not prescribed to patients with CKD G4-G5 in the United States because its use is not recommended in patients with a CL_{cr} < 30 mL/min. This recommendation stems from a lack of efficacy and safety data in this population. Duloxetine is used in patients with kidney disease outside of the United States. European Renal Best Practice and the British Columbia Renal Agency (Canada) recommend duloxetine be initiated at low doses, 30-40 mg daily, and titrated upward as tolerated in patients with CKD G4-G5 and those receiving KRT. The correct answer to question 3 is (b). It seems reasonable to initiate duloxetine at a low dose and closely monitor for side effects in patients with CKD G4-G5 who would benefit from duloxetine's additional indications.

In patients with CKD and moderate to severe pain that cannot be controlled with non-opioid alternatives, certain opioids can be used with caution. The preferred opioids in CKD include hydromorphone, fentanyl, methadone,

Table 5. Non-opioid Analgesics

Medication	Recommended Initial Dosing	Other Pearls
Acetaminophen	500-1,000 mg orally every 6 h	• Use for nociceptive pain • Maximum of 4 g/d
Capsaicin topical cream	Apply a thin layer topically 3-4×/d	• Use for localized nerve pain • Adherence can be a problem
Lidocaine 5% topical patch	Apply up to 3 patches for 12 hours per day	• Use for localized nerve pain • Patches may be cut to size
Topical NSAID (diclofenac gel)	Apply 2-4 g to affected area 4×/d	• Use for localized nerve pain • Adherence can be a problem
Oral NSAIDs	eGFR 30-60 mL/min/1.73 m^2: Short-term, as-needed use, or low doses preferred; long-term use on case-by-case basis with monitoring eGFR15-29 mL/min/1.73 m^2: case-by-case basis with close monitoring eGFR < 15 mL/min/1.73 m^2: contraindicated	• Use for nociceptive pain • Negative effects: ↑ risk for GI bleed, ↑ risk for CV adverse events, ↑ edema, ↑ hyperkalemia, worsening HTN, ↓GFR
Tricyclic antidepressants (nortriptyline and desipramine)	Nortriptyline: No adjustment needed Desipramine: Start at 25 mg 1×/d and titrate up slowly	• Use for neuropathic pain • Can lower seizure threshold • Anticholinergic side effects
Gabapentin	100-300 mg orally 1×/d titrated up to recommended dosage based on CL_{cr}	• Use for neuropathic pain
Pregabalin	25 mg orally 1-2×/d titrated up to recommended dosage based on CL_{cr}	• Use for neuropathic pain
Duloxetine	30 mg orally 1×/d Not recommended per US prescribing information for CL_{cr} <30 mL/min	• Use for neuropathic pain ◇ CL_{cr} < 30 mL/min and KRT: o ERBP recommends duloxetine at 40 mg 1x/d titrated carefully ◇ British Columbia Renal Agency recommended starting dose is 30 mg 1×/d
Venlafaxine	37.5 mg orally 1×/d	• Use for neuropathic pain

Abbreviations: CL_{cr}, creatinine clearance; CV, cardiovascular; ERBP, European Renal Best Practice; GFR, glomerular filtration rate; GI, gastrointestinal; KRT, kidney replacement therapy; HTN, hypertension; NSAIDs, nonsteroidal anti-inflammatory drugs.

and buprenorphine (Table 6). Starting with a lower dose and titrating up as needed is always recommended and immediate-release formulations are preferred over extended-release formulations due to a lower risk for accumulation. Oral or injectable hydromorphone is the preferred short-acting opioid for severe acute pain in CKD. Hydromorphone is metabolized in the liver primarily to hydromorphone-3-glucuronide, which is excreted in the urine and can accumulate in patients with CKD G4-G5. This metabolite does not have analgesic properties but has been rarely associated with myoclonus and delirium. Use hydromorphone with caution, initiating at 25% to 50% of the usual starting dose and titrating to response.

Fentanyl is a potent opioid with a short half-life. It undergoes rapid hepatic metabolism to inactive metabolites. Although injectable fentanyl is safe in CKD, its short half-life and frequent dosing makes it inconvenient for extended acute pain management. Transdermal fentanyl is an option for chronic pain management in patients with CKD. Data are lacking on its use in this population, but it appears to be safe with cautious dosing.

Methadone is both a μ-receptor agonist and a NMDA receptor antagonist. It is metabolized in the liver to inactive metabolites and is safe to use for chronic pain in patients with CKD G4-G5. Methadone can prolong the QTc interval, increasing the risk for torsades de pointes. Therefore, electrocardiographic

Table 6. Opioid Analgesics

Opioids	Dosing Issues	Comments
Preferred		
Hydromorphone	• CL_{cr} < 60 mL/min: Dose reduction (25%-50% of the usual starting dose)/extending dosing interval recommended	• Preferred short-acting opioid for severe pain in CKD • Accumulation of active metabolite hydromorphone-3-glucuronide can cause neuroexcitatory symptoms (eg, myoclonus, delirium, and seizures) • Active metabolite removed by HD
Fentanyl	• Injectable: No dosage adjustment recommended in mild-moderate CKD • Patch: Reduce dose to 75% of normal if CL_{cr} < 50 mL/min and to 50% of normal if CL_{cr} < 10 mL/min	• Inactive metabolites • $t_{1/2}$ unchanged with CKD • Not removed by intermittent HD
Methadone	• No dosage adjustment for CKD	• Not removed by intermittent HD
Buprenorphine transdermal patch	• No dosage adjustment for CKD	• Removed by intermittent HD
Not preferred		
Hydrocodone	• Hepatically metabolized to hydromorphone • Avoid extended-release formulations	• Most often prescribed in combination with acetaminophen • Use with caution
Oxycodone	• CL_{cr} < 60 mL/min: Give 50%-75% of normal dose, and consider extending the dosing intervals to every 6-8 hours • Avoid extended-release formulation	• Oxycodone and metabolite oxymorphone are renally excreted and can accumulate • Use with caution if other preferred options cannot be used • Removed by intermittent HD
Morphine	• Use IV and immediate-release oral with caution ○ CL_{cr} 30-59 mL/min: Consider alternate opioid; administer 50%-75% of usual initial dose (may also consider extending dose interval); titrate cautiously to response ○ CL_{cr} 15-29 mL/min: Avoid use; if necessary, administer 25%-50% of usual initial dose (may also consider extending dose interval) • CL_{cr} < 15 mL/min: Avoid use • Avoid using extended-release formulation	• Accumulation of active metabolites (morphine-6-glucuronide, morphine-3-glucuronide) • Use with caution, short term, in patients where preferred options cannot be used • Morphine and metabolites are removed by intermittent HD
Tramadol	• CL_{cr} < 30 mL/min: Increase dosing interval to every 12 hours; max daily dose 200 mg • Max dose in dialysis is 50 mg every 12 hours; dose after dialysis • Avoid use of extended-release formulation	• Generally, not recommended for use in CKD G4-G5 • Caution as can lower seizure threshold • Risk for serotonin syndrome • Variable effects based on slow, fast, or ultrafast metabolizers • Removed by intermittent HD

Abbreviations: CKD, chronic kidney disease; CL_{cr}, creatinine clearance; HD, hemodialysis.

monitoring of the QTc needs to occur more frequently in patients with CKD. Buprenorphine is a mixed opioid agonist-antagonist. It is mostly used for opioid addiction but is available in a transdermal patch for severe pain. It is metabolized in the liver to active metabolites that are much less potent than the parent compound and are only minimally eliminated by the kidneys. Transdermal buprenorphine appears safe in patients with CKD.

Oral oxycodone is a reasonable short-acting opioid for patients with CKD. Oxycodone is metabolized in the liver to its active metabolite oxymorphone, which can accumulate in CKD G4-G5. Reduced doses and slow titration are recommended. Morphine is metabolized to morphine-3 (MG3) and morphine-6 glucuronide (MG6), which are cleared by the kidneys and can accumulate in patients with reduced kidney function. MG3 has limited analgesic effects and more neuroexcitatory effects such as allodynia, myoclonus, and seizures. MG6 has potent analgesic effects greater than the parent compound morphine. Immediate-release oral or IV morphine should be used with caution in patients with CKD G3-G5 and only in patients where other options are not viable. The correct answer to question 4 is therefore (a).

Codeine is a weak opioid that is used as an antitussive and rarely for mild-moderate pain. Codeine is hepatically metabolized to multiple active metabolites that are cleared by the kidneys. The increased side-effect profile, individual variability in the degree of metabolism due to CYP2D6 polymorphisms, and limited analgesic benefits make codeine a poor choice for pain management, and it should be avoided in CKD. Tramadol is a weak μ-receptor agonist and a serotonin and norepinephrine reuptake inhibitor. Tramadol is metabolized by the liver to the active metabolite, O-demethyl tramadol, which is predominantly cleared by the kidneys. Metabolism is variable due to CYP-enzyme polymorphisms. It can potentiate serotonin syndrome and lowers the seizure threshold, which can be a concern in patients with CKD. Some have recommended using it with caution in CKD G4-G5 while others have recommended avoiding it entirely.

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Antibiotics

Case 5: *A 66-year-old man is admitted to the hospital with Staphylococcus aureus bacteremia without evidence of endocarditis. The culture/sensitivity report indicates that the S aureus is oxacillin sensitive. He has a medical history of uncontrolled hypertension, dyslipidemia, polycystic kidney disease, and he receives intermittent HD on a Monday-Wednesday-Friday schedule. The internal medicine team would like to switch the patient from IV vancomycin to IV cefazolin for a 4-week total course of antibiotics.*

Question 5: Which of the following should you advise the internal medicine team about the dosing of cefazolin in this patient?

a) Cephalosporins demonstrate time-dependent pharmacodynamics; therefore, reducing the maintenance dose and keeping the dosing interval close to normal is ideal.
b) Cefazolin is unique in that its prolonged half-life in patients receiving maintenance HD allows for dosing 3 times a week after dialysis.
c) Cephalosporins demonstrate concentration-dependent pharmacodynamic characteristics; therefore, keeping a normal dosing but extending the dosing interval is ideal.
d) IV vancomycin would be preferred over IV cefazolin in this patient on HD because of its more convenient dosing and the option for therapeutic drug monitoring.

For the answer to the question, see the following text.

There are several issues that practitioners should be aware of when prescribing antibiotics in patients with abnormal kidney function (Table 7). One issue is how the pharmacodynamic characteristics of the antibiotic impact how the drug should be adjusted based on kidney function. Antibiotics demonstrate either concentration or time-dependent pharmacodynamic characteristics (see Fig 1). Drug adjustments should be done to maximize these characteristics (see Fig 2). For antibiotics that exhibit time-dependent pharmacodynamics (eg, penicillins, cephalosporins, and carbapenems) it is important to maintain the drug concentration above the MIC for as long as possible. With these drugs, decreasing the dose while maintaining a normal dosing interval maximizes $AUC_{0\text{-}24}$/MIC. Exceptions include the cephalosporins cefazolin and ceftazidime. Due to their prolonged half-life in patients on maintenance HD they can be administered 3 times weekly after dialysis, which improves convenience and adherence. The correct answer to question 5 is (b).

For drugs that exhibit concentration-dependent pharmacodynamics (fluoroquinolones and aminoglycoside antibiotics), giving a normal dose with an extended dosing interval will result in higher peaks and lower troughs, which

Table 7. Intravenous Antibiotics: Pharmacodynamic Principles to Consider When Adjusting Dose

Drug Class	Drugs	Pharmacodynamic Principle	Pharmacodynamic Parameter to Optimize
Penicillins	Penicillin Piperacillin-tazobactam Ampicillin ± sulbactam Nafcillin[a]	Time dependent	Time > MIC
Cephalosporins	Cefazolin Cefuroxime Cefotetan Cefoxitin Cefotaxime Ceftazidime Ceftriaxone Cefepime Ceftolozane/tazobactam Ceftaroline	Time dependent	Time > MIC
Carbapenems	Imipenem Meropenem Ertapenem Doripenem	Time dependent	Time > MIC
Glycopeptide	Vancomycin	Time dependent	$AUC_{0\text{-}24}$/MIC
Macrolide	Azithromycin[a] Erythromycin Clarithromycin	Time dependent	$AUC_{0\text{-}24}$/MIC
Oxazolidinones	Linezolid[a] Tedizolid[a]	Time dependent	$AUC_{0\text{-}24}$/MIC
Lipopeptides	Daptomycin	Concentration dependent	$AUC_{0\text{-}24}$/MIC
Aminoglycosides	Gentamicin Tobramycin Amikacin	Concentration dependent	C_{max}/MIC; $AUC_{0\text{-}24}$/MIC
Lipoglycopeptides	Telavancin Dalbavancin Oritavancin	Concentration dependent	$AUC_{0\text{-}24}$/MIC
Fluoroquinolones	Levofloxacin Ciprofloxacin Moxifloxacin[a]	Concentration dependent	$AUC_{0\text{-}24}$/MIC; C_{max}/MIC

Abbreviations: $AUC_{0\text{-}24}$, area under the concentration-time curve during a 24-hour period; C_{max}, maximum drug concentration; MIC, minimum inhibitory concentration.
[a]Does not require dosage adjustment for kidney dysfunction

will maximize the peak concentration above the minimum inhibitory concentration (C_{max}/MIC) while minimizing side effects. Although most antimicrobials require dosage adjustments in patients with reduced kidney function, several do not have significant kidney excretion and do not require dosage adjustments in patients with abnormal kidney function. These exceptions are summarized in Table S4.

Another issue that needs to be considered in patients with reduced kidney function is the potential increased risk for side effects associated with antibiotics. If β-lactam antibiotics are not adjusted appropriately, central nervous system side effects such as confusion, myoclonus, and seizures can occur. Penicillins have been associated with impaired platelet aggregation, a rare side effect that may be more likely in patients with uremic platelet dysfunction. Carbapenems can increase seizure risk. Aminoglycosides and vancomycin (especially in combination with piperacillin) have been associated with nephrotoxicity, which is more common with high troughs, obesity, extended durations of therapy, and high daily doses. Telavancin also contains a Black Box warning regarding nephrotoxicity. Daptomycin has been associated with an increased risk for muscle toxicity (myopathy), so serum creatine kinase levels need to be monitored at least weekly or more often in patients with reduced kidney function. Fluoroquinolones carry a boxed warning regarding several toxicities such as QT prolongation, tendon rupture, peripheral neuropathy, and central nervous system and glycemic effects. Fluoroquinolones are also unique in that they can chelate with cations. Therefore, when administered orally, they need to be separated from phosphate binders and other divalent/trivalent cations.

Trimethoprim/sulfamethoxazole should be used cautiously in patients with reduced kidney function. The trimethoprim component of Bactrim is associated with hyperkalemia as it inhibits amiloride-sensitive sodium channels in the distal nephron. This can be problematic in patients CKD G4-G5. Trimethoprim is also associated with a rise in Scr due to a reduction in its tubular secretion. Although not associated with a change in GFR, it can make assessing kidney function challenging. Sulfamethoxazole, like other sulfonamides, has been associated with kidney failure due to interstitial nephritis, acute tubular necrosis, and crystalline nephropathy.

Antifungals

Most antifungals do not require dosage adjustments in patients with CKD. The injectable formulations of several of the azole antifungals should be avoided or minimized when possible in patients with CKD G3-G5 (CL_{cr} < 50 mL/min) due to the accumulation of the solubilizing agent, cyclodextrin, which can cause kidney toxicity. However, CKRT or frequent intermittent HD may be effective at removing the cyclodextrins, allowing for IV use in severely ill patients. Amphotericin B, which is used for severe invasive fungal infections, is associated with several infusion-related adverse events, but is most associated with nephrotoxicity. Amphotericin B causes tubular dysfunction, renal tubular acidosis, and afferent vasoconstriction with accompanying reduced GFR. Risk is increased with an increase in total cumulative dose and is decreased with the use of a lipid-based formulation. Flucytosine is eliminated approximately 90% via glomerular filtration. It requires dosage adjustments starting at a CL_{cr} of <40 mL/min and must be dosed after HD due to its significant removal. Due to a high rate of resistance, it is usually not given alone but in combination with amphotericin B. Fluconazole also has high kidney clearance and requires dosage adjustment when the CL_{cr} falls below 50 mL/min.

Antivirals for HIV

Case 6: *A 56-year-old man was recently started on combination antiretroviral therapy (cART) (dolutegravir/emtricitabine/tenofovir alafenamide) for newly diagnosed human immunodeficiency virus (HIV) infection. He his medical history is significant for type 1 diabetes since the age of 15, hypertension, dyslipidemia, hypothyroidism, and CKD G3aA1 (ie, urinary albumin-creatinine ratio of <30 mg/g). The patient's Scr at the start of therapy is 1.60 mg/dL. His estimated CL_{cr} is 48 mL/min using a weight of 145 lb. Two weeks after starting therapy his Scr is 1.91 mg/dL. The value is rechecked a few days later, and it is 1.82 mg/dL. There is no increase in proteinuria, and no cells or casts were noted on the urinalysis.*

Question 6: Which of the following is the most likely explanation for his increase in Scr?

a) The dolutegravir is interfering with the secretion of creatinine.
b) The tenofovir alafenamide is causing an AKI.
c) The patient's emtricitabine is worsening his CKD.
d) The increase in Scr is unlikely to be related to his cART or HIV.

For the answer to the question, see the following text.

CKD is an important comorbidity in individuals with HIV, and HIV is an independent risk factor for CKD. Although cART reduces CKD in the HIV-infected population overall, some drugs individually have been shown to be nephrotoxic and associated with worsening kidney function. Of antiretrovirals that are commonly prescribed, tenofovir disoproxil fumarate (TDF) and atazanavir have been linked to incident CKD and kidney disease progression in large cohort studies. Atazanavir can cause nephrolithiasis and acute interstitial nephritis. TDF is associated with acute tubular injury and Fanconi syndrome. Tenofovir alafenamide (TAF), a prodrug of tenofovir, can achieve higher intracellular levels and lower circulating levels of tenofovir, which is thought to decrease the risk for reduced kidney function (Fig 3). TAF appears well tolerated in individuals with CKD G1-G3a. More data are needed in CKD G4-G5.

The protease inhibitors indinavir, darunavir, and lopinavir have also been associated with crystalline nephropathy and/or nephrolithiasis. Several antiretrovirals (raltegravir, dolutegravir, and cobicistat) interfere with the secretion of creatinine through the organic cation transporter 2 and/or multidrug and toxin extrusion protein 1 (MATE1). The correct answer to question 6 is therefore (a). This interference results in a small rise in Scr and a reduction in eGFR. This effect on Scr occurs within 2 to 4 weeks of exposure, does not progress, is not associated with proteinuria, and reverses upon drug discontinuation. The KDIGO expert panel suggests that low-risk individuals (eGFR >90 mL/min/1.73 m^2, no proteinuria, age < 50 years, absence of hypertension or diabetes) can be managed with any standard cART regimen.

Most nucleoside/nucleotide analogue reverse transcriptase inhibitors are primarily excreted renally and require dosage adjustment in patients with reduced kidney function. Integrase inhibitors, nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, fusion inhibitors, and chemokine coreceptor antagonists do not require dosage adjustments for CKD G1-G3, but data are lacking in CKD G4-G5. In addition, some protease inhibitors and the NNRTI nevirapine may need dosing modifications in patients on HD, and the chemokine coreceptor antagonist maraviroc should not be given to patients with CKD G4-G5 who are receiving a potent CYP3A inhibitor or inducer.

Antivirals for Hepatitis C

Chronic hepatitis C virus (HCV) is associated with worsening kidney function and increased mortality in dialysis patients. The newest medications recommended for all HCV genotypes have increased the sustained viral response rates to >95% for most patient populations and may improve mortality in patients with CKD G4-G5. Elbasvir/grazoprevir, glecaprevir/pibrentasvir, sofosbuvir/velpatasvir, and sofosbuvir/ledipasvir have all been studied in CKD patients, including patients on HD. Current recommended regimens do not require dosage adjustment in patients with reduced kidney function. The most up-to-date recommendations from the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) for HCV treatment in CKD

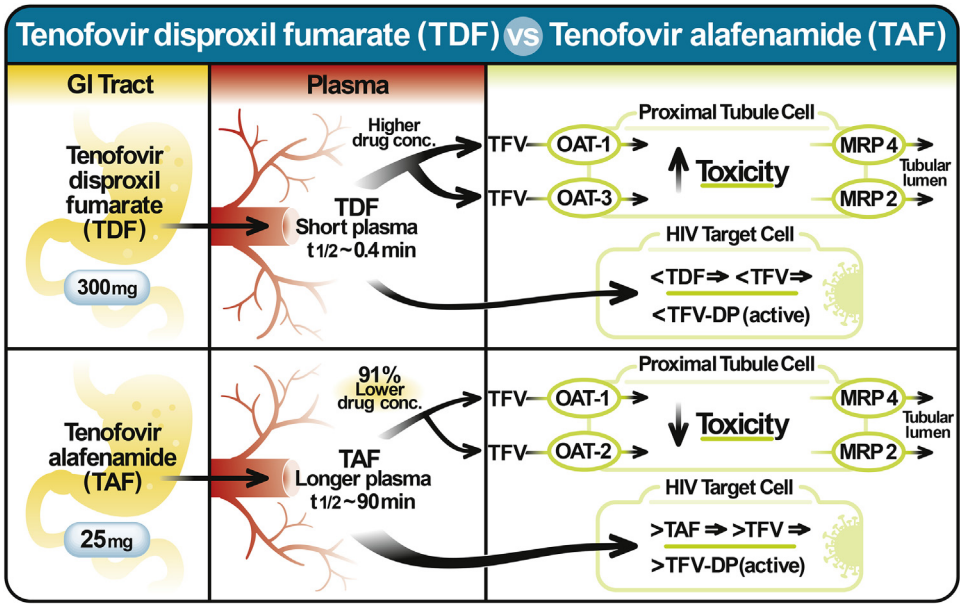

Figure 3. Differences between tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide (TAF) with regard to serum levels, intracellular levels, and potential for kidney toxicity. Abbreviations: Conc., concentration; OAT, organic anion transporter; MRP, multidrug resistance protein; TVF, tenofovir; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate.

patients can be found at https://www.hcvguidelines.org/unique-populations/renal-impairment.

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Conclusion

Designing appropriate medication regimens in patients with kidney disease is a complex and dynamic process, and recent cross-sectional studies have highlighted the high incidence of inappropriate prescribing. Nephrologists are in a prime position to evaluate and understand the degree of kidney function and the implications for medication selection and dosing. Understanding general pharmacokinetic and pharmacodynamics concepts can assist nephrologists with rational drug recommendations, whether they are serving as the primary physician or a consultant to another service. The nephrologist plays an important role in both the inpatient and outpatient settings by identifying the highest-risk medications and making appropriate medication alterations that will maximize benefit while reducing the risk of patient harm.

Supplementary material

Supplementary File (PDF)

Item S1: Limitations of kidney function estimates for drug dosing in CKD.

Item S2: Antidiabetic agents.

Item S3: Antihypertensives.

Item S4: Anticoagulant agents.

Table S1: Recommendations for management of patients with atrial fibrillation.

Table S2: Secondary renal outcomes of SGLT2 inhibitors from cardiovascular and heart failure outcomes trials.

Table S3: Outcomes trials of SGLT2 inhibitors in patients with CKD.

Table S4: Antimicrobials that do not require dosage adjustments.

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