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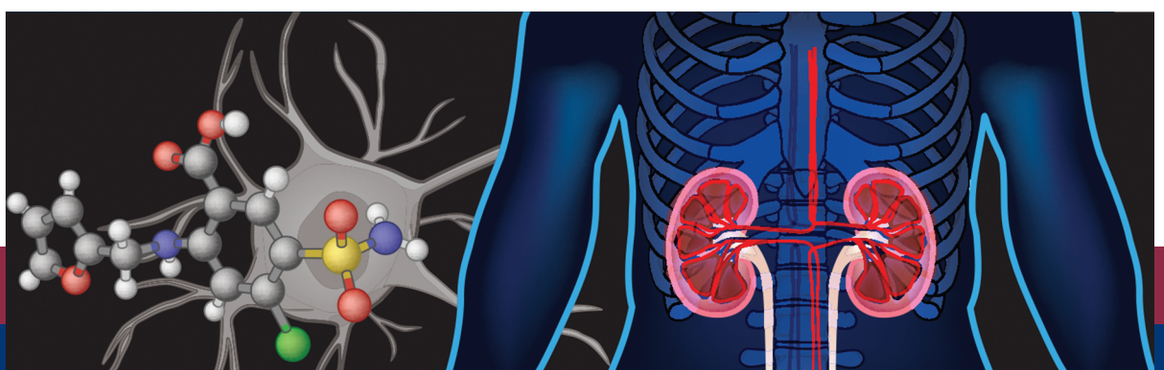

Nephropharmacology

Update for the Clinician

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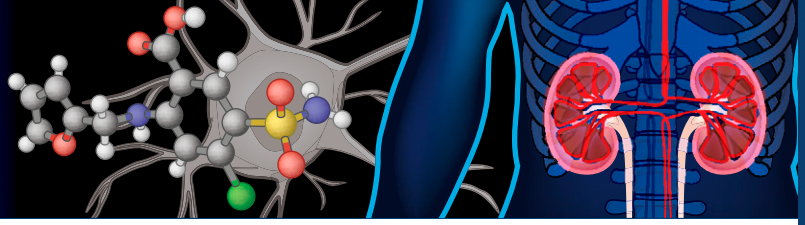
for the Clinician



Introduction to Nephropharmacology for the Clinician
A New *CJASN* Series

Thomas D. Nolin[1] *and Mark A. Perazella*[2,3]

Clin J Am Soc Nephrol 13: 1083–1084, 2018. doi: https://doi.org/10.2215/CJN.03180318

Drugs form the cornerstone of treatment for a plethora of diseases, including kidney disease and its common comorbid conditions. Patients with kidney disease are routinely prescribed numerous drugs simultaneously. For instance, patients with CKD not dependent on dialysis are prescribed a mean of six to 12 medications (1), whereas patients with ESKD take a median number of 19 pills per day, with 25% of patients with ESKD taking >25 medications daily (2). Hospitalized patients with AKI are also exposed to a large number of medications. Several factors affect the clinical pharmacology of drugs in humans, including pharmacokinetics, pharmacogenetics, and pharmacodynamics (Figure 1). Impaired kidney function leads to changes in pharmacokinetics and pharmacodynamics; thus, commonly used drugs frequently exhibit altered risk-benefit profiles in patients with CKD (3). Unfortunately, clinical trials are notorious for excluding patients with kidney disease (4,5), often leading to a lack of data to inform drug selection and dosing and forcing clinicians to extrapolate clinical data derived from the general population to patients with CKD. It is no surprise then that patients with CKD experience increased rates of adverse drug events and toxicity compared with those with normal kidney function (6). There is even less pharmacologic data available to clinicians on patients with AKI (7). These issues underscore the importance of "Nephropharmacology for the Clinician," the latest educational series to appear in the *Clinical Journal of the American Society of Nephrology* (*CJASN*).

We believe that this series fills an important gap in the nephropharmacology literature, providing reviews of topics that generally fit into four categories (Table 1). The series begins with this issue of the *CJASN*, providing the first of several reviews covering basic principles of clinical pharmacology in kidney disease, including clinically applied pharmacokinetics, pharmacodynamics, and pharmacogenomics. The second group of reviews relates to fundamentally important pharmacologic considerations in kidney disease, including kidney function estimates for drug dosing, medication safety principles, common drug nephrotoxicities, and use of technology to prevent nephrotoxicity. Underpinning the series is a collection of reviews that comprise the third group and present clinical pharmacologic aspects of commonly used drug classes from a nephrocentric perspective. The series concludes with reviews of emerging issues in nephropharmacology, including use of biosimilars and the regulatory perspective on drug development.

The editors have assembled a team of highly regarded physicians, clinical pharmacologists, researchers, and regulatory scientists to contribute to this important educational series. The reviews are intentionally brief but comprehensive, contemporary, and clinically applied. We anticipate that the series will be a vital resource for clinical practitioners and trainees alike related to basic

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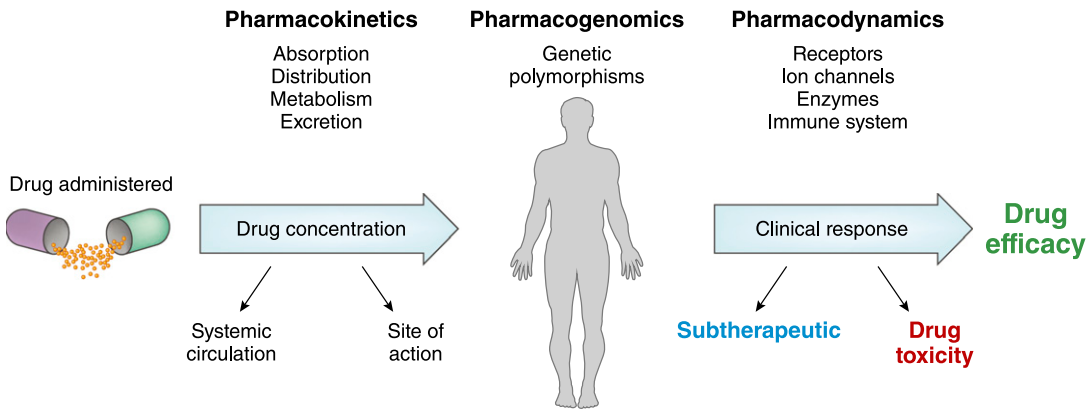

Figure 1. | **Several factors affect clinical pharmacology in humans.**

Table 1. Topics to be included in the educational series "Nephropharmacology for the Clinician"

Review Categories and Topics
Basic principles
Pharmacokinetics
Pharmacodynamics
Pharmacogenomics
Fundamentally important considerations in nephropharmacology
Kidney function estimates for drug dosing
Medication safety principles and practice
Pharmacology behind common drug nephrotoxicities
EMR alerts to prevent drug nephrotoxicity
Contemporary perspectives on drug use in kidney disease
Pain management
Anticoagulants
Diuretics
Antihypertensives
HIV therapy
Antibiotics
Emerging topics
Biosimilars
Regulatory perspective

EMR, electronic medical record.

principles and considerations that are fundamentally important in the use of drugs in patients with kidney disease.

Disclosures

None.

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See related article, "Clinical Pharmacokinetics in Kidney Disease: Fundamental Principles," on pages 1085–1095.

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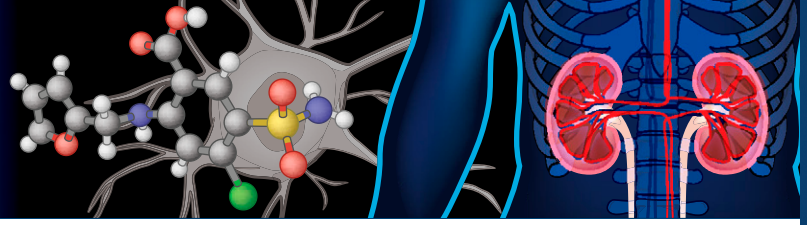

Clinical Pharmacokinetics in Kidney Disease
Fundamental Principles

Tom N. Lea-Henry,[1,2] *Jane E. Carland,*[3,4] *Sophie L. Stocker,*[3,4] *Jacob Sevastos,*[4,5] *and Darren M. Roberts*[2,3,6]

Abstract
Kidney disease is an increasingly common comorbidity that alters the pharmacokinetics of many drugs. Prescribing to patients with kidney disease requires knowledge about the drug, the extent of the patient's altered physiology, and pharmacokinetic principles that influence the design of dosing regimens. There are multiple physiologic effects of impaired kidney function, and the extent to which they occur in an individual at any given time can be difficult to define. Although some guidelines are available for dosing in kidney disease, they may be on the basis of limited data or not widely applicable, and therefore, an understanding of pharmacokinetic principles and how to apply them is important to the practicing clinician. Whether kidney disease is acute or chronic, drug clearance decreases, and the volume of distribution may remain the same or increase. Although in CKD, these changes progress relatively slowly, they are dynamic in AKI, and recovery is possible depending on the etiology and treatments. This, and the use of kidney replacement therapies further complicate attempts to quantify drug clearance at the time of prescribing and dosing in AKI. The required change in the dosing regimen can be estimated or even quantitated in certain instances through the application of pharmacokinetic principles to guide rational drug dosing. This offers an opportunity to provide personalized medical care and minimizes adverse drug events from either under- or overdosing. We discuss the principles of pharmacokinetics that are fundamental for the design of an appropriate dosing regimen in this review.

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Introduction
Drugs are an important and frequently used treatment for patients with kidney disease. Knowledge of basic pharmacokinetic principles is important for all prescribers, but it is particularly important for nephrologists and other physicians who routinely see patients with organ dysfunction that affects drug handling.

Prescribing to patients with kidney disease is complicated, because kidney disease has multiple effects on pharmacokinetics, and these effects are dependent on both the drug and the clinical context. For example, kidney disease may be chronic (slowly progressive over months or years) or acute (rapidly evolving), and each scenario requires a different approach to drug dosing. Understanding how changes to physiology affect the pharmacokinetics of a given drug is essential to rational drug use and the optimization of treatment regimens.

Failure to properly account for the effect of kidney disease when designing appropriate drug-dosing regimens can predispose an individual to treatment failure or adverse drug events. Guidelines for adjustment of the dosing regimen in varying stages of CKD are provided by the manufacturer.

Furthermore, dose recommendations in the setting of kidney disease are frequently on the basis of limited data, and they may not adequately account for interindividual variability or acute changes, such as during AKI. For example, between 2002 and 2007, only 57% of new drug applications to the Food and Drug Administration (FDA) examined pharmacokinetics in kidney impairment, and only 44% of those with data in kidney impairment evaluated patients on hemodialysis (1). This reflects the FDA policy that manufacturers are not required to determine the effect of kidney disease on drug dosing (2).

In many cases, it is reasonable to simply prescribe the dose recommended by the manufacturer, particularly if the drug has a wide therapeutic index, the duration of therapy is short, the dose is low (*e.g.*, prophylaxis dosing), and/or there is the ability to titrate the dose on the basis of clinical and laboratory progression. Other dosing guidance is available through textbooks, online references, and local procedures for many drugs but not all, and there may be significant differences in the suggested change in dose between different resources (3). Unfortunately, limited data or other safety concerns may simply lead the manufacturer to declare that the drug is contraindicated in patients with advanced kidney disease, which can deprive patients with kidney disease of important drug options.

In recent years, the application of pharmacokinetic principles to drugs in the postmarketing phase has raised the prospect of using drugs that were previously considered contraindicated in patients with eGFR<30 ml/min per 1.73 m^2, including metformin (4) and novel-acting oral anticoagulants (NOACs) or direct-acting oral anticoagulants (DOACs; for

example, apixaban) (5). There may also be circumstances when additional adjustments to the dosing regimen may be required in a patient (for example, a change in clearance due to a coprescribed drug that induces or inhibits elimination pathways of the index drug).

Therefore, it is necessary to have a rational approach to prescribing in patients with kidney disease. This requires knowledge about pharmacokinetic principles, properties of the drug, and how the drug will be handled by an individual patient. The purpose of this review is to provide an overview of pharmacokinetic principles that affect the design of a dosing regimen and provide the basis for discussions regarding the delivery of personalized medicine to those with kidney disease.

Relationship between Dosing Regimen and the Effect of a Drug

An individual's response to a drug is determined by both the pharmacokinetics and pharmacodynamics of that drug. Pharmacodynamics is concerned with the effect of the drug on the body, including interactions between the drug, its target, and downstream biochemical effects. Pharmacokinetics describes the effect of the body on a drug and reflects the physiologic processes of absorption, distribution, metabolism, and excretion. Each of these processes may be altered in patients with kidney disease and affect therapeutic outcomes.

The concentration-time profile of a drug reflects the net effects of these pharmacokinetic processes after drug administration (Figure 1). The concentration-time profile approximates the clinical effect of most drugs, and drug exposure relates to the maximum plasma concentration (Cmax) and/or the area under the concentration-time curve (AUC). In general, high drug exposures increase the risk of adverse drug reactions, and low drug exposures are ineffective.

When the changes in pharmacokinetics due to kidney disease and other conditions are understood, the dosing regimen can be adjusted so that the concentration-time profile is optimized for the individual.

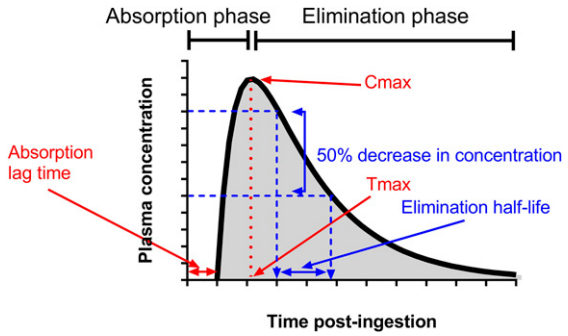


Figure 1. | Plasma concentration-time profile after oral administration of a single dose. The components relevant to the pharmacokinetics of a drug's concentration-time profile are the peak or maximum plasma concentration (Cmax) and the time when it occurs (Tmax), the area under the concentration-time curve (represented as shaded area), and the elimination $t_{1/2}$ (determined using the blue lines).

Reasons to Optimize Dosing Regimens

Either sub- or supratherapeutic dosing can occur when appropriate dose adjustments are not made in patients with kidney disease, and both have negative effects on patient outcomes, including morbidity, prolonged hospital admissions, and potentially, death. Subtherapeutic dosing increases the risk of treatment failure, which may be life threatening (*e.g.*, anti-infectives) or organ threatening (*e.g.*, immunosuppressive drugs). The risk of supratherapeutic exposure from drugs (or their active or toxic metabolites) that rely on kidney elimination is amplified when the drug has a narrow therapeutic index, such as digoxin or lithium. In many cases, accumulation develops over weeks, and the onset of drug toxicity is insidious. These principles are reflected in the examples below.

Selected Examples of Drugs That Require Special Consideration When Prescribing to Patients with Kidney Disease

Antibiotics

The efficacy of antibiotics depends on their concentration relative to the minimum inhibitory concentration (MIC) of the culprit bacteria. Three pharmacokinetic-pharmacodynamic targets describe features of the concentration-time profile that maximize antibiotic efficacy.

(*1*) The ratio of maximum free drug plasma concentration to MIC (concentration dependent; *e.g.*, aminoglycosides)
(*2*) The ratio of the AUC to MIC (AUC:MIC; *e.g.*, vancomycin)
(*3*) The proportion of time that the plasma concentration exceeds the MIC (time-dependent killing; *e.g.*, β-lactam antibiotics)

Therefore, the actual target depends on the specific antibiotic and the MIC of the culprit bacteria (6). Plasma concentrations below the target concentration predispose to therapeutic failure and development of multiresistant organisms. Although prescribing higher doses increases the likelihood of achieving pharmacokinetic-pharmacodynamic targets, it also increases the risk of adverse events, including in drugs considered to have a wide therapeutic index, like β-lactam antibiotics (7).

Lithium and Digoxin

Lithium excretion depends on kidney function. The most common cause of adverse reactions to lithium is chronic poisoning, which typically occurs in the setting of reduced kidney function as a result of dehydration or dose adjustment with inadequate monitoring (8,9). The resultant neurotoxicity can be severe and persist for days or weeks, and in rare instances, it can be irreversible (9).

Similarly, digoxin has a narrow therapeutic index and accumulates when there is impaired kidney function if the dose is not decreased (10). Digoxin poisoning is reasonably common, being associated with prolonged hospital admissions and high resource utilization, including antidigoxin Fab (11).

Both agents commonly undergo therapeutic drug monitoring, and the frequency at which this occurs should be increased in settings where the drug clearance (CL) is significant reduced or where this fluctuates, as in AKI.

Cyclophosphamide

Cyclophosphamide is used to treat various autoimmune diseases and malignancies, and much of the effect of cyclophosphamide occurs through CYP450-mediated formation of active metabolites, which are eliminated by the kidney. Thus, active dose reductions are performed in patients with impaired kidney function (*e.g.*, plasma creatinine concentration >300 μmol/L [12]) in autoimmune disease and oncology (13) to limit the accumulation of cyclophosphamide and active metabolites (13,14). Cyclophosphamide bioactivation may increase in patients with GN compared with those with other types of kidney disease, which may prompt different approaches to dose adjustment (15). Inadequate dose reductions of cyclophosphamide in CKD may contribute to the increased adverse events and death in patients with systemic vasculitis in the first 12 months of treatment (16). However, studies have also highlighted that low-dose cyclophosphamide reduces treatment efficacy in, for example, the treatment of lupus nephritis (17). Therefore, more research is required to determine how to optimize cyclophosphamide therapy in patients with CKD, which ideally incorporates both pharmacokinetic and pharmacodynamic measures of effect.

Metformin

Metformin is the first-line oral antihyperglycemic drug for type 2 diabetes mellitus. However, its use was formerly considered to be contraindicated in patients with CKD due to concerns around metformin-associated lactic acidosis. Metformin-associated lactic acidosis is attributed to metformin accumulation in the context of impaired kidney function, and it is characterized by severe lactic acidosis (18,19). Regardless, preliminary studies have shown that metformin can be safely prescribed to patients with advanced CKD after appropriate dose reduction (4,20), increasing the treatment options for these patients.

Novel-acting/Direct-acting Oral Anticoagulants

The increasing use of NOACs/DOACs has presented issues for patients with both acute kidney disease and CKD, and NOACs/DOACs were previously contraindicated in advanced CKD. There is variability in the extent to which CL of these drugs depends on kidney function, such that kidney disease has differing effects on drug exposure and the risk of adverse events. For example, dabigatran pharmacokinetics is largely dependent on kidney CL and P-glycoprotein transporters, and very significant increases in AUC can occur with progressive decline in kidney function (21), predisposing to adverse events. In comparison, there is less of a decrease in the CL of apixaban from advanced kidney disease, and after studies on the basis of core pharmacokinetic principles, an appropriate dose reduction was determined and tested (5), providing guidance for its use in patients who are dialysis dependent (22). However, data about interindividual variability are still limited for these drugs, and therefore, there may be circumstances where therapeutic drug monitoring may be beneficial.

Pharmacokinetic Principles and Parameters

Quantifying changes in pharmacokinetics allows the dosing regimen to be adjusted with some precision to maximize the likelihood that the desired drug concentration-time profile is achieved. CL and volume of distribution (Vd) are the primary pharmacokinetic parameters that determine the concentration-time profile (drug exposure) and therefore, the appropriate dosing regimen (more discussion is in part 2 [23]). Patients with kidney disease are particularly susceptible to changes in both CL and Vd in both chronic and acute conditions. Half-life ($t_{1/2}$) is a widely used pharmacokinetic parameter, which depends on both CL and Vd, and therefore, it is referred to as a secondary parameter (Equation 5).

Absolute Bioavailability

Absolute bioavailability is the fraction of drug that reaches the systemic circulation after administration, and it is calculated by comparing the AUC of an administered dose with the AUC achieved after rapid intravenous infusion (Equation 1). This is most commonly thought of in terms of oral bioavailability, where an orally administered drug's bioavailability depends on the extent of gastrointestinal absorption and hepatic first-pass elimination:

$$F=(AUC_{po}\times D_{iv})/(AUC_{iv}\times D_{po}), \quad (1)$$

where F is the absolute bioavailability, AUC_{po} is the AUC with oral dosing, AUC_{iv} is the AUC with intravenous dosing, D_{po} is the oral dose administered, and D_{iv} is the intravenous dose administered.

The principles can also be used to quantify the effect of kidney disease on drug exposure. Several processes involved in drug absorption and hepatic metabolism are affected by kidney disease (Table 1), but the significance of these changes for a given drug is not well defined. Indeed, the relative influence of bioavailability and/or CL on a change in the AUC cannot be readily differentiated in many instances. However, if an increase in AUC is mostly due to an increase in bioavailable dose, then the Cmax and AUC would be expected to increase to a similar extent (Equation 2). For example, in Figure 5A, the effect of a 50% decrease in CL is that the Cmax increased 20% and the AUC increased 100%, which is consistent with the relationship shown in Equation 6 rather than an increase in bioavailable dose (Equation 2). Clinical applications of this in patients with kidney disease are discussed in part 2 of this series (23).

Volume of Distribution (Vd)

Vd is an apparent (theoretical) volume rather than being a true entity. It is the parameter relating the concentration of a drug in the plasma to the total amount of the drug in the body. It is quantified as liters per kilogram body weight, and it is mostly determined by the distribution and binding of the drug to extravascular tissues compared with plasma proteins. Vd is also used to estimate the Cmax (Figure 1) after a single dose, and it influences the loading dose (equation 1 in part 2 of this series in ref. 23) and $t_{1/2}$ (Equation 5).

After a rapid bolus dose, the Cmax is predicted by Equation 2, where F is bioavailability (F=1 after intravenous administration; discussed above and in Equation 1):

$$C\,max=\frac{Dose\times F}{Vd}. \quad (2)$$

Vd is highly dependent on not only body mass but also, body composition, notably the absolute and relative

Table 1. Changes in pharmacokinetics in patients with CKD (15,36,46,47)

Process	Example Drugs	Anatomic Location	Alteration to This Process in CKD	Potential Change in Kinetics with CKD	Potential Implications for Dosing Regimen
Absorption and bioavailability					
Passive: concentration-dependent absorption	Multiple	Enterocytes	Decrease or increase	Decreased or increased bioavailability	Increased or decreased dose
Enzymatic metabolism (multiple; in particular, CYP3A4)	See below	Enterocytes	Decreased	Increased bioavailability	Decrease in dose
Active: P-glycoprotein (ABCB1)	Calcineurin inhibitors, digoxin, methotrexate	Enterocytes	Decreased	Increased bioavailability	Decrease in dose
Distribution					
Passive: concentration-dependent diffusion	Multiple	Systemic	No change or increased	No change or increased	No change or increase in initial dose
Protein binding	Multiple	Systemic	Decrease in protein concentration or protein binding	Increase in free (unbound) fraction, which can increase clearance and distribution	Potential increase in dose and either increase or decrease in frequency depending on change in Vd relative to CL
Active transporters (P-glycoprotein; ABCB1)	See above	Liver, brain, elsewhere	Unknown	Decreased activity: increased Vd	No change or increase in initial dose
Drug Clearance					
Passive: glomerular filtration	Multiple, including methotrexate	Glomerulus	Decreased	Decreased clearance	Decrease maintenance dose or frequency of dosing
Active: organic anion transporting polypeptide	β-Lactam antibiotics, methotrexate, atorvastatin, imatinib, rosuvastatin	Brain, liver, kidneys, intestine	Decreased	Decreased clearance	Decrease maintenance dose or frequency of dosing
Active: organic cation transporter	Metformin	Liver, kidney, brain, lung, *etc.*	Decreased	Decreased clearance	Decrease maintenance dose or frequency of dosing
Active: P-glycoprotein (ABCB1)	See above	Liver, kidney	Unknown (decreased in rats)	Decreased clearance	Decrease maintenance dose or frequency of dosing
Enzymatic: CYP2C8/9[a]	S-Warfarin, fluoxetine, tamoxifen, glipizide	Liver	Decreased or no change	Decreased clearance	Decrease maintenance dose or frequency of dosing
Enzymatic: CYP2C19[a]	Citalopram, cyclophosphamide, warfarin, diazepam	Liver	Decreased or no change	Decreased clearance	Decrease maintenance dose or frequency of dosing

Table 1. (Continued)

Process	Example Drugs	Anatomic Location	Alteration to This Process in CKD	Potential Change in Kinetics with CKD	Potential Implications for Dosing Regimen
Enzymatic: CYP2D6[a]	Carvedilol, metoprolol, tramadol, tamoxifen, codeine	Liver	Decreased	Decreased clearance	Decrease maintenance dose or frequency of dosing
Enzymatic: CYP3A4/5[a]	Atorvastatin, verapamil, tacrolimus, fluconazole, cyclophosphamide, carbamazepine, tolvaptan	Liver, enterocytes, kidneys (CYP3A5)	Decreased or no change	Decreased clearance	Decrease maintenance dose or frequency of dosing
Enzymatic: CYP1A[a]	Caffeine, theophylline, warfarin	Liver	Decreased or no change	Decreased clearance	Decrease maintenance dose or frequency of dosing
Enzymatic: CYP2B6[a]	Cyclophosphamide, bupropion, methadone	Liver, kidney	Increased or decreased	Increased or decreased clearance	Increase or decrease maintenance dose or frequency of dosing

Vd, volume of distribution;
[a]The effect of CKD on the expression and activity of some cytochrome P450 isoenzymes is controversial and may instead reflect changes in transporter function as discussed in the text. Rowland Yeo *et al.* (45) found a reduction in cytochrome P450 activity across a range of isoenzymes. However, although some studies have identified progressive reductions in clearance by individual isoenzymes (for example, CYP2D6 [46]), others have found no difference in enzyme activity in advanced CKD for CYP3A4/5 (16,46) and CYP2C9 (47–50). Additional studies in human subjects are required to clarify the extent of any effect.

amounts of body water and adipose tissue. In the clinical circumstance where there is an increase in Vd (*e.g.*, severe nephrotic syndrome), this can require a proportional increase in the dose to achieve the same Cmax. Conversely, changes in drug bioavailability may require a change in the dose, and bioavailability can increase or decrease in kidney disease, which is discussed later and in Table 1. Clinical applications of this are discussed in part 2 of this series (23).

Clearance

CL is the volume of blood cleared of a drug in a period of time usually measured in units of liters per hour or milliliters per minute, and it is the parameter that most closely describes drug elimination. CL determines the maintenance dose rate of a drug required to achieve a target plasma concentration (and therefore, effect) at steady state.

CL can be referred to by a particular organ (*e.g.*, liver or kidney), a particular metabolic pathway, or the whole body. The total or systemic CL is the sum of the CL by individual organs, which incorporates both active (*e.g.*, metabolism or active secretion) and passive (*e.g.*, glomerular filtration) processes, as follows:

$$CL = CL_K + CL_H + CL_{other}, \quad (3)$$

where CL_K is kidney clearance, CL_H is hepatic clearance, and CL_{other} accounts for other routes of drug elimination (for example, kidney replacement therapy or metabolism by circulating esterases). The sum of CL_H and CL_{other} is sometimes referred to as nonrenal CL. The relationship between different routes of CL is shown graphically in Figure 2, where the anticipated change in total CL is related to GFR. Although this is a convenient way to think about changes in pharmacokinetics in the setting of kidney dysfunction, it can be an oversimplification for some drugs, because changes in nonrenal drug CL occur at the same time, which is discussed in detail below and represented in Figure 3.

Kidney Clearance. The traditional way to determine kidney CL is to measure the rate of excretion of the drug in urine and changes in the drug plasma concentration at the same time. Kidney CL is the net result of three different processes: filtration at the glomerulus, active secretion in the proximal tubule, and passive reabsorption along the kidney tubules:

$$CL_K = (Fu \times GFR) + CL_{secretion} - CL_{reabsorption}, \quad (4)$$

where Fu is the fraction of the total drug concentration that is unbound to plasma proteins (free), $CL_{secretion}$ is due to active secretion in the kidney tubules, and $CL_{reabsorption}$ refers to reabsorption from the glomerular filtrate back to the circulation.

Glomerular filtration varies with kidney blood flow, which can decrease when there is a reduced cardiac output or volume depletion. However, for some drugs, active

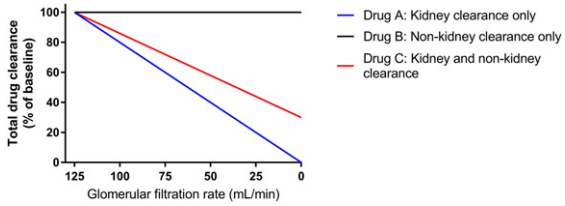


Figure 2. | Changes in total drug clearance with declining kidney function relates to the extent of drug clearance by the kidney. Representation on the basis of Equation 3 for drugs with three different pharmacokinetic profiles. Here, Drug A is 100% cleared by the kidney, and therefore, it is predicted that a 50% decrease in GFR will correlate with a 50% decrease in total clearance, prompting a 50% decrease in dose or doubling of the dosing interval to maintain the same mean plasma concentration. Drugs from many classes can be represented: for example, antibiotics (A: β-lactams or aminoglycosides, B: macrolides, and C: fluoroquinolones), anticoagulants (A: dabigatran, B: warfarin, and C: rivaroxaban), and β-blockers (A: atenolol, B: metoprolol, and C: bisoprolol). Unfortunately, this representation is an oversimplification, because it does not consider changes to nonrenal clearance in kidney disease that occur with some drugs as discussed in the text.

secretion is significant, and therefore, the kidney CL exceeds GFR (for example, metformin, meropenem, amoxycillin, cefalexin, ampicillin, and piperacillin). The relative contributions of the processes shown in Equation 4 are illustrated in Figure 4, and Table 1 summarizes the more common drug transporters that contribute to this phenomenon.

Furthermore, as GFR declines, the extent to which total kidney CL of a drug depends on active secretion can increase. Active transporters are also important, because

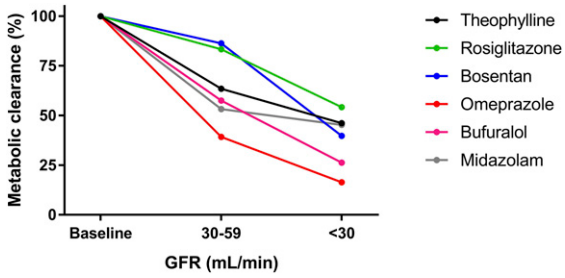


Figure 3. | Drug clearance by metabolism can also decrease with declining kidney function. Drawn from data presented by Rowland Yeo *et al.* (45), the analyses are of clearance data in clinical studies after correcting for differences in protein binding and blood to plasma partitioning. The drugs were chosen as a probe of different CYP450s (theophylline for 1A2, rosiglitazone for 2C8, bosentan for 2C9, omeprazole for 2C19, bufuralol for 2D6, and midazolam for 3A4). Although these data are illustrative, the effect on expression and activity of some cytochrome P450 isoenzymes is controversial. For example, some studies have identified progressive reductions in clearance by CYP2D6 (46), whereas others have found no difference in enzyme activity in advanced CKD for CYP3A4/5 (16,46) and CYP2C9 (47). Instead, the changes in metabolic clearances noted in CKD may also relate to changes in expression or function of drug transporters (for example, those on the hepatocyte cell membrane). Additional studies in human subjects are required to further clarify the extent of any effect.

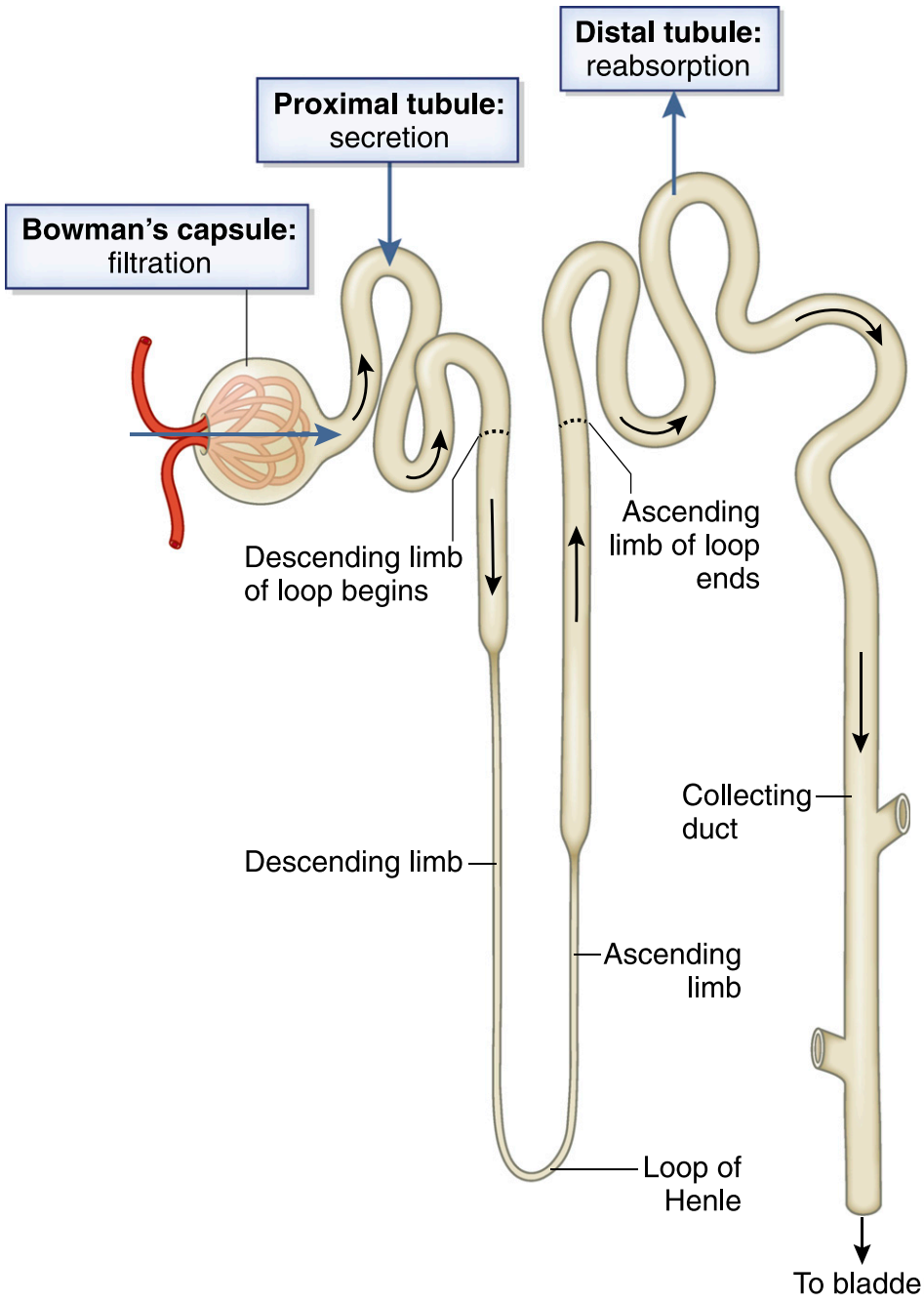
drug-drug interactions may decrease CL due to competitive binding and being a saturable process. The clinical implication of this for drugs that are substrates of drug transporters in the kidney is that greater dose reductions are required in patients with kidney tubulopathy compared with those with a similarly reduced GFR due solely to glomerulopathy (24). In the case of glomerulopathy, drug CL may be preserved relative to the reduced GFR by preservation of active tubular secretion of drugs and/or metabolites (25,26). This is contrary to the intact nephron hypothesis that assumes that drug CL has a linear relationship to GFR, because reductions in kidney function are caused by a reduction in the number of intact (complete) nephrons. Furthermore, drug transporter activity can be pH dependent (for example, the active secretion of metformin is reduced when the filtrate in the tubular lumen is alkaline [27,28], which has the potential to decrease kidney CL). This challenges the use of GFR as the sole criterion for estimating kidney CL of drugs.

Finally, some drugs are reabsorbed from the glomerular filtrate in the tubules, and the extent of reabsorption can vary with urine pH and flow (*e.g.*, weak acids, such as salicylate or some herbicides), knowledge of which has been used in the treatment of poisoning (29). The effect of kidney disease on tubular reabsorption and the implications on drug dosing are poorly defined.

Nonrenal Clearance. There can be an apparent increase in nonrenal CL in patients with kidney disease, which probably reflects increased opportunity for elimination by alternative CL mechanisms or possibly, upregulation in other CL processes. For example, lower proportions of the dose of meropenem and piperacillin are eliminated in urine in patients with CKD compared with that predicted from data in healthy subjects (30,31), which is not consistent with Equation 3 or Figure 2.

However, for some drugs, nonrenal CL is decreased in the context of kidney disease, although most of these data are in the setting of CKD rather than AKI. The proposed mechanism for decreased nonrenal CL is inhibition of enzymes and transporters by circulating uremic toxins, which can be reversed (corrected) with their removal by hemodialysis (32). Here, the $t_{1/2}$ decreases (rectifies) when affected drugs are administered immediately after hemodialysis (33). This is supported by *in vitro* studies (34–36), with some exceptions (37), and therefore, other mechanisms may also contribute, such as changes in protein expression (36,38). Of note, inhibition of drug transporters may decrease nonrenal drug CL due to either decreased secretion (*e.g.*, P-glycoprotein, organic anion transporting polypeptide, or organic cation transporter) or uptake into hepatocytes (*e.g.*, organic anion transporting polypeptide or organic cation transporter). The extent to which kidney disease decreases the CL of selected drugs that are substrates of the cytochrome P450 isoenzyme system is shown in Figure 3 and Table 1, potentially reflecting changes in both enzyme and transporter activity.

Another factor to consider when interpreting nonrenal drug CL data is the decrease in protein binding that occurs in CKD and the limited data describing changes in free (unbound compared with total) drug CL. For example, research describing the effect of CKD on benzodiazepine hepatic CL noted a decrease in CL of the free fraction in



Kidney clearance of example drugs in patients with normal kidney function

Drug	Proportion filtered at the glomerulus	Proportion secreted in the proximal tubule	Proportion reabsorbed in the distal tubule	Total kidney clearance (mL/min)
Benzylpenicillin (48)	30–50%	50–70% (OATP)	Uncertain	500
Metformin (49)	30–50%	50–70% (OCT)	Uncertain	500
Fluconazole (50)	100%	Nil	80–90%	15

OATP, organic anion transporting polypeptide; OCT, organic cation transporter

Figure 4. | Total kidney clearance is dependent on the contributions of each of glomerular filtration, secretion in the proximal tubule, and reabsorption in the distal tubule. OATP, organic anion transporting polypeptide; OCT, organic cation transporter.

only two of nine studies, whereas in some studies, there was an increase in CL (32).

Despite these complexities, a common method to estimate the change in total drug CL between specific patient populations is to quantify the change in the function of the organ that has a significant role in the total drug CL (for example, determining kidney function by estimating GFR for a drug that is predominantly cleared by the kidney). Subsequently, using Equation 3, one can estimate the percentage change in drug CL in those with kidney

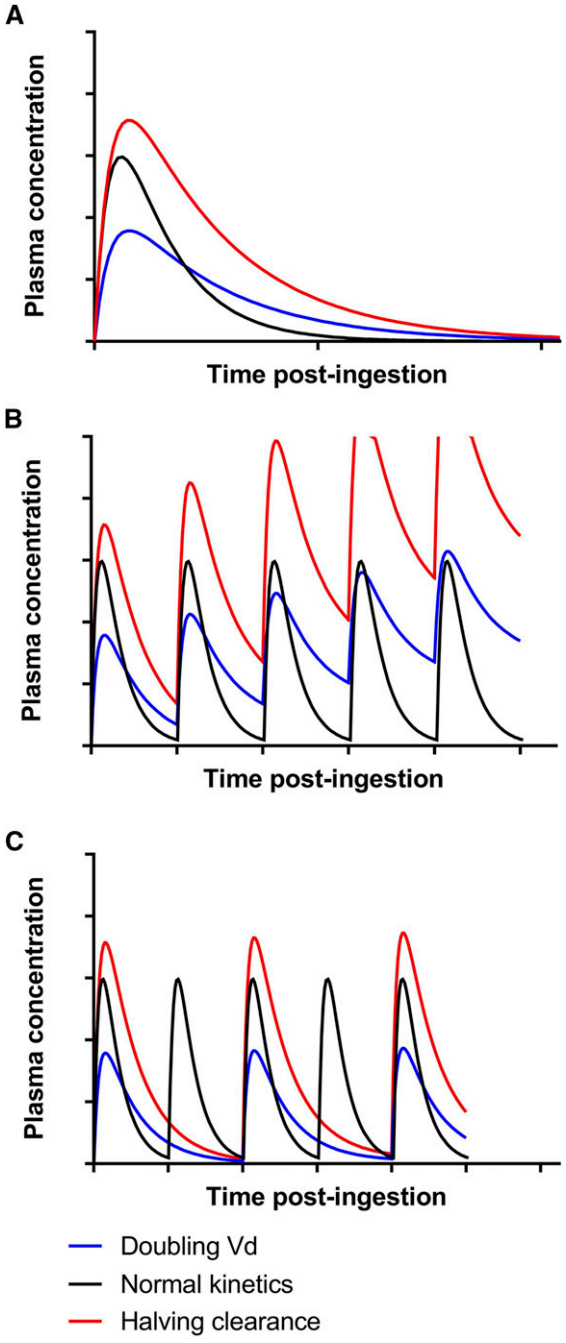


Figure 5. | A change in either volume of distribution or clearance has differing effects on the concentration-time profile. Graphs are drawn to scale for ready comparison. (A) A doubling in volume of distribution (Vd) and a halving of clearance have the same effect on the elimination $t_{1/2}$, but they incur substantially different concentration-time profiles. Halving clearance leads to a doubling of the area under the concentration-time curve (Equation 6). The doubling in Vd leads to a reduction in maximum plasma concentration (Equation 2) but no change in the area under the concentration-time curve, despite the change in the concentration-time profile. (B) In patients with altered kinetics, continuous dosing will lead to drug accumulation if the regimen is not adjusted. Onset of toxicity will occur earlier from a decrease in clearance. (C) In patients with altered kinetics, increasing the dosing interval will prevent drug accumulation. Here, because the $t_{1/2}$ was doubled in both cases, the dosing interval was also doubled. Although the trough concentrations are similar after the decrease in dosing frequency, the maximum plasma concentration and average concentration are lower when Vd is doubled, which may decrease the effectiveness of this regimen compared with in a patient with normal kinetics.

impairment relative to healthy subjects. Drug CL relative to kidney function can be found in some textbooks and reviews (for example, ref. 39 for antibiotics). Where possible, it is preferable to understand how total CL changes with decreasing kidney function or consider the change in $t_{1/2}$, because this incorporates both CL and Vd (Equation 5). Another factor that may limit the precision with which GFR reliably estimates drug CL includes the interindividual variability in pharmacokinetics. The clinical applications of the changes in CL are discussed further in part 2 of this series (23).

Elimination $t_{1/2}$

The elimination $t_{1/2}$ is the time required for the plasma concentration to decrease by 50% (Figure 1). $t_{1/2}$ is determined in an individual by measuring the rate of decrease in serial (a minimum of three where possible) plasma drug concentrations. Plasma sampling can occur soon after an intravenous dose or in the case of orally administered drugs, after completion of absorption (after Cmax or Tmax) (Figure 1).

$t_{1/2}$ is a major determinant of the duration of action after a single dose, the time required to reach steady-state plasma concentrations (obtained approximately 4–5 $t_{1/2}$ after drug initiation) with multiple doses, and the dosing frequency. It is important to recognize that the time to reach steady-state concentration will be delayed for drugs with relatively prolonged half-lives.

$t_{1/2}$ incorporates both Vd and CL:

$$t_{1/2} = \frac{0.693 \times \text{Vd}}{\text{CL}}. \quad (5)$$

$t_{1/2}$ is prolonged in proportion to an increase in Vd or a decrease in CL. For example, the $t_{1/2}$ will double after either a 50% decrease in CL or doubling of Vd (Figure 5A). Failure to dose adjust in the case of impaired kidney CL will lead to drug accumulation and risk of toxicity (Figure 5B), especially for chronic drug therapy. An example of this is the use of atenolol in patients with ESKD, in whom the $t_{1/2}$ increases from 6 to 100 hours compared with in patients with preserved kidney function (40). A change in either CL or Vd has a very different effect on the concentration-time profile (Figure 5, A and B), but in each case, the dosing interval should be doubled (Figure 5C). However, Figure 5 is probably an oversimplification, because both CL and Vd can change in acute and chronic clinical situations, such as sepsis, kidney disease, and liver disease.

Finally, the $t_{1/2}$ to consider is not only that of the parent drug, but also that of active or toxic metabolites. There are many cases of poisoning occurring due to accumulation of metabolites that are eliminated by the kidney, such as morphine causing coma, meperidine (pethidine) causing seizures, allopurinol causing toxic epidermal necrolysis, glyburide (glibenclamide) causing hypoglycemia, and cyclophosphamide causing immunosuppression. For example, relative to patients with normal kidney function, active cyclophosphamide metabolites had a significantly prolonged $t_{1/2}$ and accumulated in a patient with a creatinine clearance of 18 ml/min, which contributed to prolonged bone marrow suppression (41) (discussed in Examples of Drugs That Require Special Consideration When Prescribing to Patients with Kidney Disease).

Area Under the Curve (AUC)

For a given dose, the AUC is proportional to the decrease in CL. This relationship between AUC and CL is expressed by Equation 6:

$$\text{AUC} = \frac{\text{Dose}}{\text{Clearance}}. \quad (6)$$

Changes in drug CL as the result of kidney disease can, therefore, increase the AUC and overall drug exposure for a given dose, which in turn, increases the risk of adverse drug reactions. Numerically, this can be quantified using the equation

$$\Delta\text{AUC} = \frac{\text{AUC2}}{\text{AUC1}}, \quad (7)$$

where AUC1 is the initial or baseline AUC (*e.g.*, with normal kidney function or before an intervention) and AUC2 is the observed AUC after the change (*e.g.*, with kidney disease or after the intervention). For example, a 50% decrease in CL will double the AUC (ΔAUC=2, 100% increase, or twofold increase), which is shown graphically in Figure 5A.

When Should the Usual Dosing Regimen Be Adjusted?

The minimum change in kidney function that necessitates a change in dosing is not well defined. A long-standing rule of thumb is that dose adjustment is not required if a pharmacokinetic parameter changes by <30% (42), but this threshold is conservative. An FDA draft document recommends that detailed pharmacokinetic studies should be performed if kidney disease has a "substantial effect" on pharmacokinetics (for example, the drug exposure expressed as the AUC [Figure 1], increases by at least 50%–100%) or less effect if the drug has a narrow therapeutic range compared with in healthy subjects (2). When comparing the same dose, an increase in AUC is usually proportional to the decrease in CL (Equations 6 and 7). Therefore, a decrease in kidney function is unlikely to be clinically significant if drug clearance decreases by less than 50% (the "no effect boundary").

The extent to which drugs (or their relevant metabolites) are excreted by the kidney are also important in determining whether dose adjustment is necessary in kidney disease. In general, dose adjustment is unlikely to be required when <30% of a dose is excreted by the kidneys (2). It is also important to consider instances where dose adjustments for primarily hepatically metabolized drugs may be required, because their pharmacologically active and/or toxic metabolites are primarily excreted by the kidney, which may increase the pharmacologic effect and/or risk of adverse events. For example, morphine is metabolized to morphine-6-glucuronide (up to 360 times more potent than the parent drug [43]), which is cleared by the kidney and accumulates in kidney failure. Mycophenolate is metabolized to mycophenolic acid glucuronide (inactive), which is cleared by the kidney, and it can accumulate in kidney impairment and may contribute to the gastrointestinal intolerance of this medication seen in severe CKD (44).

Other considerations include the risk of drug accumulation and the clinical manifestations when this occurs. For example, dose adjustments are less necessary for a low-toxicity drug being prescribed for a short course of treatment (*e.g.*, an

oral penicillin), where the risk of accumulation is mitigated by the short duration of therapy (for example, several days). In contrast, dose adjustments are required for drugs with a long treatment duration and a higher intrinsic toxicity (*e.g.*, metformin, digoxin, lithium, or colchicine) (discussed in Examples of Drugs That Require Special Consideration When Prescribing to Patients with Kidney Disease), particularly if they have a long elimination $t_{1/2}$ (*e.g.*, >24 hours).

Therefore, dose adjustments may be required for selected drugs with pharmacokinetics that change significantly in kidney disease, particularly if there is a high risk of drug accumulation and severe and/or irreversible toxicity. Methods for dose adjusting in patients with kidney disease are discussed in detail in part 2 of this series (23).

Conclusions

Pharmacokinetic factors that inform the dosing of drugs are well described. However, limited data in patients with kidney disease, particularly for certain drugs, and marked interindividual variability complicate the development of dosing guidelines. Furthermore, kidney disease can cause wide-ranging changes in pharmacokinetics through derangement of not only kidney drug CL but also, nonrenal CL, Vd, and bioavailability. These considerations apply to both the parent drug and any active or toxic metabolites. Each requires a different approach to adjustment of the dosing regimen, and inappropriate adjustments, particularly with maintenance therapy, lead to drug concentrations that are too low or too high, predispose patients to harm due to therapeutic failure, or adverse drug reactions.

Drug dosing can be optimized on a case by case basis by the use of rational dose design grounded in an understanding of basic pharmacokinetic concepts and therapeutic drug monitoring, particularly for drugs that have a narrow therapeutic index. This is a key component in the development of personalized medical care for patients with kidney disease, and it is discussed further in part 2 of this series (23).

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Disclosures

None.

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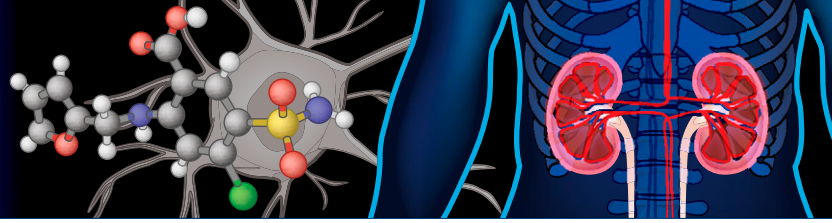

Clinical Pharmacokinetics in Kidney Disease
Application to Rational Design of Dosing Regimens

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Abstract

A change in pharmacokinetics can alter drug exposure and predispose the patient to either over- or underdosing, potentially resulting in adverse drug reactions or therapeutic failure. Kidney disease is characterized by multiple physiologic effects, which induce clinically significant changes in pharmacokinetics. These vary between individuals and may be quantitated in certain instances. An understanding of pharmacokinetic concepts is, therefore, important for a rational approach to the design of drug dosing regimens for the delivery of personalized medical care. Whether kidney disease is acute or chronic, drug clearance decreases and the volume of distribution may remain unchanged or increase. AKI is defined by dynamic changes in kidney function, which complicates attempts to accurately quantify drug clearance. In contrast, changes in drug clearance progress more slowly with CKD. In general, kidney replacement therapies increase drug clearance, but the extent to which this occurs depends on the modality used and its duration, the drug's properties, and the timing of drug administration. However, the changes in drug handling associated with kidney disease are not isolated to reduced kidney clearance and an appreciation of the scale of potential derangements is important. In most instances, the first dose administered in patients with kidney disease is the same as in patients with normal kidney function. However, in some cases, a higher (loading) initial dose is given to rapidly achieve therapeutic concentrations, followed by a lower maintenance dose, as is well described when prescribing anti-infectives to patients with sepsis and AKI. This review provides an overview of how pharmacokinetic principles can be applied to patients with kidney disease to personalize dosage regimens. Patients with kidney disease are a vulnerable population and the increasing prevalence of kidney disease means that these considerations are important for all prescribers.

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Introduction

Pharmacokinetic concepts underlie the rational prescribing of drugs. Drugs are commonly prescribed in the management of patients with both chronic and acute kidney disease, and this population may have an increased risk of adverse drug reactions (1). Kidney diseases cause a range of changes to pharmacokinetics, as discussed in part 1 of this series (2), so these must be considered when designing appropriate dosage regimens.

The usual method of dosage adjustment in patients with kidney disease is defined by the product label, but this can have limitations. During drug development, dosing regimens are initially determined in patients with normal or mildly impaired kidney function. The drugs are then trialed in a smaller number of patients with more severe kidney disease before registration. Data for patients with ESKD treated with dialysis are particularly limited before registration, with only a minority of new drug applications to the US Food and Drug Administration (FDA) being evaluated in this patient population (3). Indeed, because of complex pharmacokinetics in a small number of cases or other safety concerns, manufacturers may recommend that the drug is contraindicated in patients with advanced kidney disease, hindering access to a potentially beneficial drug.

As discussed in part 1 (2), although there are guidelines available for dosage adjustment in patients with kidney disease, these guidelines may be inconsistent (4) or not applicable to all clinical contexts, particularly in AKI where drug clearance can change rapidly.

A common approach to drug dosing when there is uncertainty in its dosage or pharmacokinetics in patients with kidney disease is to use a conservative "start low and go slow" iterative approach. Depending on the rate of dose escalation, this approach will attain a target clinical effect (*e.g.*, BP or glycosylated hemoglobin A_{1c}) in a delayed fashion, which is reasonable for drugs that yield a clinical benefit from treatment over months or years (*e.g.*, antihypertensives or oral hypoglycemics). However, this approach is less useful for drugs requiring a rapid onset of effect, such as anti-infective or immunosuppressive drugs. Antibiotics are inappropriately dosed in patients with decreased GFR, and this may contribute to poorer outcomes in those requiring kidney replacement therapy (5,6).

The purpose of this review is to provide an overview of how the pharmacokinetic principles outlined in part 1 of this series (2) can be applied to patients with kidney disease to personalize dosage regimens and to appropriately monitor drug therapy. It should,

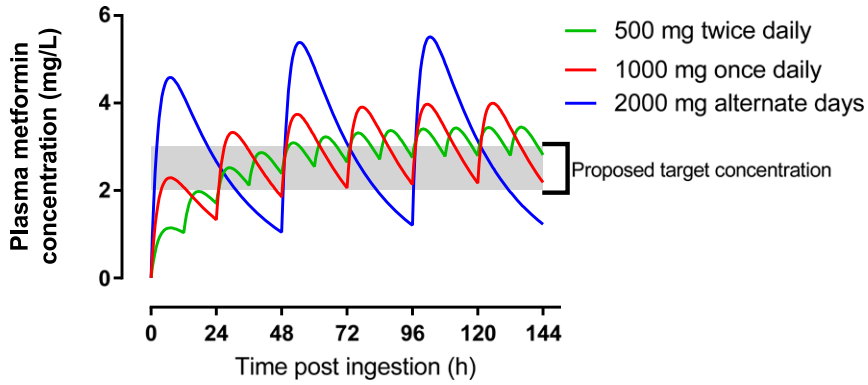

Figure 1. | The same daily dose of metformin administered as different dosage regimens has differing effects on the concentration–time profile in a patient with CKD. Three different dosage regimens (each equivalent to 1000 mg/d) are simulated in a patient with an GFR of 20 ml/min. The concentration–time profiles are shown relative to a proposed target concentration of 2–3 mg/L. This dosage is anticipated to be an overdose on the basis of a suggested initial dose of 750 mg/d for patients with an GFR of 30 ml/min (42). Each regimen achieves steady-state concentrations within 70 hours and the same average plasma concentration, but more frequent dosing is associated with less variability in plasma concentration (the difference between *C*max and the minimum plasma concentration).

therefore, be possible to optimize drug therapy in this vulnerable patient population, utilizing this knowledge both at the bedside and when designing research projects.

Rational Design of Dosing Regimens

General Principles

The important principles to consider include the therapeutic target, the initial dose, the maintenance dose, the dose frequency, and when a dosage adjustment should be performed. The key changes in pharmacokinetics that occur in a patient with kidney disease have been discussed elsewhere (2).

These principles require the prescriber to obtain published pharmacokinetic data from patient populations with similar causes of kidney disease, its severity, and manifestations, to the patient receiving treatment. Appropriate data are often difficult to ascertain, and assumptions are commonly required to assess their clinical applicability. Furthermore, interpatient pharmacokinetic variability exists, present even in apparently homogenous patient populations. This is further complicated in a cohort of patients with CKD, which incorporates a heterogeneous mix of etiologies. So, although the methods described below appear somewhat precise, there are substantial and unpredictable errors within the calculations that warrant close monitoring. Fortunately, many of the drugs currently used have a good safety profile, and therapeutic drug monitoring (TDM) is (or should be) performed for drugs requiring more precision.

Defining the Therapeutic Target

Prescribing a dose that maximizes benefits and minimizes risks is the goal of rational drug dosing. Serum drug concentration targets are derived from concentration–efficacy and/or concentration–toxicity relationships and may reflect a therapeutic target or the avoidance of drug accumulation and adverse events (Figure 1). The specific therapeutic target (optimal plasma concentration range) depends on the drug being prescribed, and sometimes on

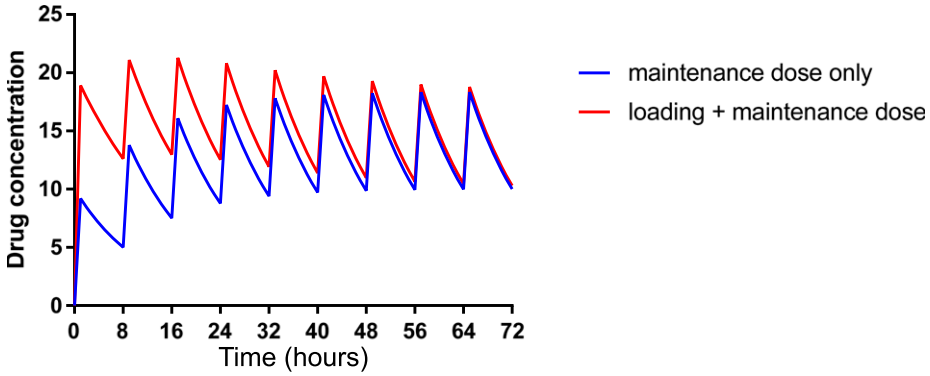

Figure 2. | A loading dose decreases the time to achieve the target concentration. When the plasma $t_{1/2}$ is prolonged (for example, because of kidney disease), the time to reach steady state or the target concentration increases proportionally. Administration of a loading dose reduces the time to achieve the therapeutic plasma concentration, and in this simulation the loading dose is double the maintenance dose.

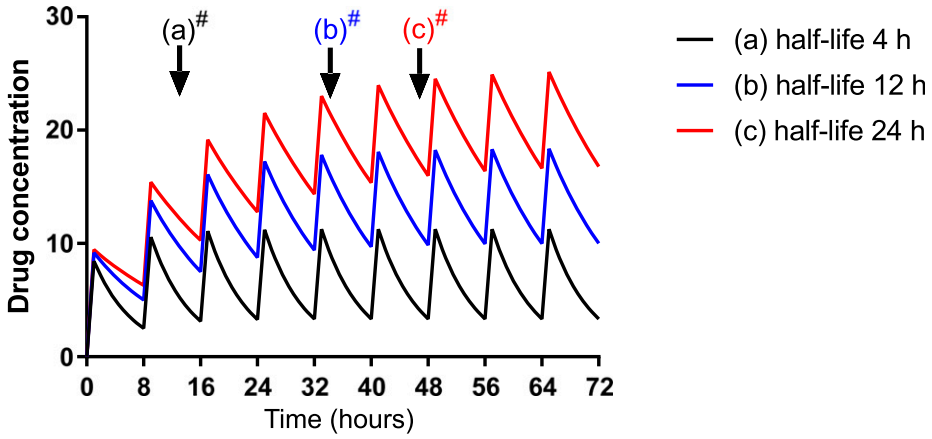

Figure 3. | An increase in a drug's $t_{1/2}$ prolongs the time to achieve steady-state plasma concentrations with maintenance dosing. The effect of the same dose given to three simulated patients with CKD. The increasing elimination $t_{1/2}$ are because of decreasing endogenous clearance, which is noted with increasing severity of CKD. Increasing the $t_{1/2}$ delays the time to steady-state plasma concentrations and results in higher plasma concentrations. Failure to reduce the dose or frequency in patients with the longer $t_{1/2}$ may predispose to adverse drug reactions. # indicates the time when steady-state conditions are achieved for the respective profile. These conditions are present when the concentration–time profile plateaus, for example, when the *C*max (maximum plasma concentrations) are no longer increasing.

the indication and individual being treated and the intended duration of therapy. In many instances, it is possible to measure not only the pharmacokinetic outcomes but also the desired therapeutic outcomes in both the short- and long-term. For example, changes to an antidiabetic regimen can be readily measured by monitoring plasma glucose concentration, as well as a long-term assessment of the effect on hemoglobin A_{1c}.

Some drugs, such as anti-infectives, immunosuppressants, and chemotherapy, are prescribed to maximize the effect of the initial dose, although the full therapeutic benefit may not be observed for days, weeks, or even months. Antibiotics also need to target a concentration–time profile related to the markers of bacterial susceptibility, such as the minimum inhibitory concentration. For other drugs, a reasonable starting point is to prescribe a dosage regimen that will target the mean or median drug concentration that was demonstrated to be effective in clinical trials. These and other examples are discussed in more detail in part 1 of this series (2).

Equations

Pharmacokinetics is a quantitative science, meaning that each parameter can be measured. These data can be incorporated into relatively simple equations to determine a dosing regimen.

Loading Dose. A loading dose is a deliberately larger initial dose given to a patient to rapidly attain a target concentration (Figure 2). This may be used in cases when there is an expanded apparent volume of distribution (*Vd*) (for example, sepsis or nephrotic syndrome) or where a delayed onset of action may be detrimental (for example, waiting until steady-state plasma concentrations are achieved with long $t_{1/2}$ drugs), as discussed in part 1 of this series (2) and reiterated in Figure 2. Because the aim of the loading dose is to achieve a target serum concentration after the first dose, changes in drug clearance do not influence the loading dose given (Equation 1). Therefore, in circumstances where no other pharmacokinetic parameters are changed, a reduction in drug clearance by the kidney does not alter the loading dose given. The loading dose is proportional to the *Vd* and is calculated by rearranging the equation for determining maximum plasma concentration (Cmax) from part 1 (2) (where *LD* is loading dose and *F* is bioavailability),

$$LD\ (\text{mg}) = \frac{\text{target concentration}\ \left(\text{mg}/\text{L}\right) \times Vd\ (\text{L})}{F}. \quad \text{(Equation 1)}$$

Maintenance Dose. For drugs administered as multiple doses, the maintenance dose depends on clearance (where MD is maintenance dose):

$$MD\,(\text{mg/h}) = \text{clearance}(\text{L/h}) \times \text{target concentration}\,(\text{mg/L}). \quad \text{(Equation 2)}$$

A potential complexity with Equation 2 is determining drug clearance in an individual patient at the time of prescribing, which is discussed in part 1 (2) and below for each patient group.

This maintenance dose is directly applied to continuous intravenous infusions. For intermittent dosing, the maintenance dose to be administered over the desired dosing interval is

$$MD\ (\text{mg/dose}) = MD\,(\text{mg/h}) \times \text{dosing interval}\,(\text{h/dose}). \quad \text{(Equation 3)}$$

A decrease in drug clearance with kidney disease prompts a decrease in either the maintenance dose or an increase in the dosing interval (Equations 2 and 3). The dosing frequency depends on the toxicity profile of the drug. For example, a relatively long dosing interval will require a relatively high *C*max to maintain an acceptable mean drug concentration (Figure 1). Therefore, in most instances, a reduction in dose rather than an increase in the dosing interval is appropriate,

Table 1. Biochemical and clinical markers of a potentially clinically significant decrease in drug clearance by the kidney

Minimum criteria that indicate the potential for impaired kidney function as proposed by the Extracorporeal Treatments in Poisoning (EXTRIP) group
eGFR<45 ml/min per 1.73 m^2
Stage 2 or 3 AKI
In adults without a baseline plasma creatinine, plasma creatinine >2 mg/dl (176 μmol/L) in adults or >1.5 mg/dl (132 μmol/L) in the elderly or those with low muscle mass
Plasma creatinine greater than two times the upper limit of normal for age and weight in children without a baseline plasma creatinine concentration
The presence of oligoanuria

with the uncommon exception of drugs where high peak serum concentrations are beneficial, such as ciprofloxacin.

As the decrease in clearance also prolongs the elimination $t_{1/2}$ (Equation 4 from part 1 [2]), the time until achieving steady state (achieved after 3–5 times the $t_{1/2}$) is delayed compared with patients with normal kidney function (Figure 3).

Design of Dosing Regimens in Patients with Kidney Disease

Kidney disease encompasses a heterogeneous range of conditions of differing severity, but also differing effects on the kidney vasculature, glomeruli, and tubulointerstitium. Each condition and corresponding treatment(s) have the potential to exert different effects on a drug's pharmacokinetics.

Criteria that indicate the potential for a clinically significant decrease in kidney function due to either AKI or CKD were proposed by the Extracorporeal Treatments in Poisoning (known as EXTRIP) group (see Table 1). These criteria were proposed to aid bedside decision-making for the treatment of poisonings, such as lithium (7), methanol (8), and metformin (9), but the underlying considerations are similar to those for therapeutic drug dosing. It is important to note that these criteria have not been validated.

CKD

CKD is a progressive decline in GFR such that kidney function is reasonably stable over weeks or months. Drug absorption from the gastrointestinal tract may be highly variable in patients with CKD. Although it is commonly thought that absorption decreases in edematous states because of gut wall edema, animal and human studies indicate that drug absorption may actually increase because of impairment of the gut wall barrier function or a decrease in function and/or expression of efflux transporters, such as P-glycoprotein (10). Furthermore, for drugs with a low bioavailability because of hepatic first-pass metabolism, the decrease in cytochrome-P (CYP) 450 enzyme and transporter activity (see part 1 [2]) may increase bioavailability. For example, significant increases in both the area under the concentration–time curve and Cmax have been demonstrated for both dihydrocodeine and repaglinide in patients with advanced CKD (Figure 4) (11,12). It is important to be cognizant of this phenomenon when prescribing these and other drugs. However, it is not clear how applicable these data are to other patients, so increased monitoring is required. The complexities of interpreting changes in area under the concentration–time curve and Cmax with regards to reduced clearance or increased bioavailability are discussed in part 1 of this series (2).

An expansion in *Vd* is reported with advanced CKD because of subsequent fluid retention, hypoalbuminemia, and decreased protein binding. However, *Vd* may also decrease in the context of sarcopenia, which is more

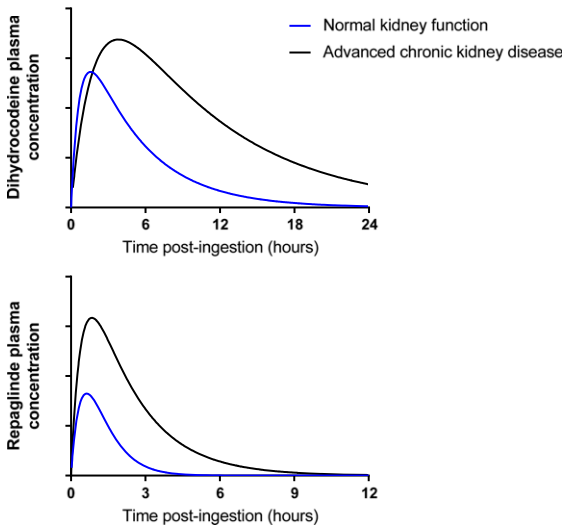

Figure 4. | Dose adjustments in patients with CKD are based on the change in the concentration-time profile for the drug of interest. Compared with patients with no kidney disease, those with advanced CKD receiving oral dihydrocodeine (upper panel; substrate of CYP2D6 and CYP3A4) showed a decrease in clearance and an increase in the mean area under the concentration–time curve and *C*max of 70% and 29%, respectively. To achieve concentrations similar to those in patients without kidney disease, the dosing interval should be prolonged but the dose does not need to be changed. In contrast, for oral repaglinide (lower panel; substrate of CYP3A4, CYP2C8, and organic anion transporting polypeptide OATP1B1, in patients with advanced CKD the mean area under the concentration–time curve and *C*max increase 232% and 82%, respectively compared with patients with no kidney disease. Here, to achieve plasma concentrations similar to those in patients without kidney disease, both the dosing interval should be prolonged and a lower dose should be prescribed. Figure panels are approximate representations of data published by Barnes *et al.* (11) and Marbury *et al.* (12).

Table 2. AKI, CKD, and from kidney replacement therapy have differing effects on pharmacokinetics

Pharmacokinetic Parameter	AKI	CKD	Kidney Replacement Therapy
Absorption	Poorly quantified, may decrease	Poorly quantified, may increase or decrease	Limited effect
Volume of distribution	No change or increase	No change or increase	No change or decrease
Metabolism	Poorly quantified, clearance by CYP3A4/5 may decrease	Decreased clearance by several CYPs observed	May increase post-KRT compared with pre-KRT, but the duration and extent of the change is poorly quantified
Excretion	Kidney: decreased, rapidly changing Nonkidney: unknown	Kidney: decreased, relatively stable Nonkidney: poorly quantified, possibly decreased	Kidney: no change Nonkidney: uncertain
Elimination			Increased because of drug removal by KRT the extent depends on properties of both the drug, the KRT regimen and its duration

CYP, cytochrome-P 450 enzyme.

common with advanced CKD. Overall, the change in *Vd* from interdialytic weight gain is low relative to total body water and is not clinically significant. The effect of severe edema on *Vd* is inconsistent, with studies finding that *Vd* could either double (13) or remain unchanged (14) in the setting of marked extracellular fluid expansion. Fluid overload is more likely to affect the *Vd* of hydrophilic drugs (for example, aminoglycoside, β-lactam, and glycopeptide antibiotics) compared with lipophilic drugs, but these rules are not always applicable.

The decrease in GFR with CKD decreases kidney drug clearance. A practical approach to adjusting drug doses in CKD is to assume that kidney drug clearance will decrease in proportion to GFR, and that nonkidney clearance is unchanged (see Figure 2 in part 1 [2]). However, this otherwise convenient approach is limited by changes to nonkidney clearance that occur with kidney disease and are difficult to quantify at the individual level (2). It also ignores the role of intact kidney tubules in the handling of many drugs and that tubular elimination likely increases relative to glomerular clearance in some types of kidney disease. For example, kidney clearance is 25% lower in patients with CKD involving tubular dysfunction relative to those with isolated GN (15).

In patients with GN, proteinuria, and hypoalbuminemia but creatinine clearance (CrCL) >90 ml/min, apparent clearance of fexofenadine (substrate of P-glycoprotein and other transporters) is decreased 40% compared with healthy controls with a comparable GFR (16). Further, the elimination $t_{1/2}$ of fexofenadine is prolonged in patients with GN compared with patients with ESKD and healthy controls, suggesting an increased *Vd* with GN (16). Yet, flurbiprofen (CYP2C9 substrate) had similar pharmacokinetics in patients with GN and CrCL>90 ml/min as in patients with ESKD. Rosiglitazone clearance is increased three-fold in patients with FSGS and nephrotic-range proteinuria despite normal eGFR, compared with healthy controls (17). Therefore, it is not possible to generalize these findings of altered pharmacokinetics to patients with different GFRs, kidney diseases, or other drugs, but the general principles are summarized in Tables 2 and 3.

AKI

AKI commonly occurs in critically ill patients. Here, dosage adjustments are complicated because of multiple marked and dynamic changes in physiology, including organ dysfunction and volume status. Subsequently, drug concentrations can either increase or decrease if the dose is not properly adjusted. For example, AKI is a common consequence of bacterial sepsis and a substantial proportion of critically ill patients receive inadequate antibiotic concentrations within the critical first 48 hours of treatment (18,19). Although some drugs used for chronic conditions can be withheld in the context of AKI (20), others such as anticoagulants, immunosuppressants, antihyperglycemics, and analgesics are often continued. In each case, dosage adjustment is required to limit the risk of adverse effects without compromising efficacy.

The *Vd* often increases in AKI; for example, in critically ill patients with sepsis and AKI, antibiotic *Vd* varies ten-fold or more (21). This occurs because of intravenous fluid loading during resuscitation, vasoplegia, and capillary leak causing edema, pleural effusions, or ascites, as well as changes in protein binding (22).

The RIFLE (Risk, Injury, Failure, Loss, ESKD) and AKIN (AKI Network) criteria categorize AKI severity on the basis of the increase in plasma creatinine concentration or decrease in urine output, but they do not quantify GFR. Changes in creatinine lag behind those of GFR (23), and intravenous fluids and dialysis temporarily decrease the plasma creatinine concentration, understating the severity of AKI. Alternatives methods to quantitate changes in kidney function in AKI include an abbreviated CrCL in patients without anuria over 2–12 hours (24), or measuring GFR using an exogenous compound; however, these only determine kidney function at a single time point. The rate of increase in creatinine plasma concentration is a further alternative (25,26), but is uncommonly used.

Table 3. AKI, CKD, and kidney replacement therapy have differing effects on drug dosing

Dosage Component	AKI[a]	CKD[a]	Kidney Replacement Therapy
Initial dose and need for a loading dose, see Equation 1	Potential changes to oral bioavailability are bypassed with intravenous administration.	Potential changes to oral bioavailability are bypassed with intravenous administration.	Rarely required in addition to those for AKI or CKD, which are the indications for KRT.
	A loading dose may be required in patients with sepsis and marked fluid overload, particularly for hydrophilic drugs that require a rapid onset of effect, such as antibiotics.	A loading dose may be required in some patients, but clinical indicators are poorly defined. Consider for hydrophilic drugs that require a rapid onset of effect, such as antibiotics.	
	Decreased clearance prolongs the time to achieve steady-state concentrations, which may prompt a loading dose.	Decreased clearance prolongs the time to achieve steady-state concentrations, which may prompt a loading dose.	
Maintenance dosage, see Equations 2 and 3	Kidney excretion decreases by ≥50%[b]: decrease amount or frequency of dose proportionally. Dose-adjustments are required frequently in response to changes in GFR.	Kidney excretion decreases by ≥50%[b]: decrease amount or frequency of dose proportionally.	Intermittent hemodialysis is efficient but usually of short duration. It has a minimal effect when the drug is administered after the treatment.
	Kidney excretion decreases by <50%[b]: no change.	Kidney excretion decreases by <50%[b]: no change.	Continuous KRT often requires an increase in maintenance dosing. However, the extent of change varies markedly depending on the drug, KRT regimen, and endogenous clearance.
	Limited data regarding dose-adjustment for drugs with predominantly nonkidney excretion.	Reductions may be required for drugs predominantly secreted in the proximal tubule in patients with kidney tubulointerstitial disease, regardless of GFR.	Peritoneal dialysis has minimal additional effects on chronic drug therapy.
	Therapeutic drug monitoring can assist dosage adjustment.	Dosage reductions may be required for drugs that undergo predominantly nonkidney clearance when GFR<60 ml/min, but data are limited or contradictory.	Therapeutic drug monitoring can assist dosage adjustment.
		Therapeutic drug monitoring can assist dosage adjustment.	

[a]A 50% decrease in GFR is chosen because this decrease has the potential to be clinically significant in most instances.
[b]To estimate the decrease in kidney excretion for a drug at a point in time, multiply the decrease in GFR by the proportion that is eliminated by the kidney. For example, for a drug that is 50% eliminated by the kidney, GFR would need to be around 1 ml/min for there to be a 50% net decrease in kidney drug clearance.

AKI decreases kidney drug clearance, which prompts a reduction in the maintenance dose (Equations 2 and 3). Unfortunately, the principles discussed for CKD cannot be readily applied to AKI because drug clearance (and distribution) vary widely in short time frames (over hours or days) and it is difficult to practically quantify GFR (21,22). Wide interpatient pharmacokinetic variability also means that extrapolation from other studies is not always possible. For example, in patients with sepsis treated with moxifloxacin, the mean clearance and *Vd* were similar to healthy patients, but interpatient variability in clearance (up to 60%) and *Vd* (30%) was greater in patients with sepsis (27). Furthermore, changes in the clearance of β-lactam antibiotics correlate poorly with fluctuations in CrCL (28). Thus, TDM is the best way to ensure the attainment of pharmacokinetic targets in AKI.

There are limited data about the effect of AKI on nonkidney clearance, but the clearance of midazolam (CYP3A4/5 substrate) is noted to decrease in AKI, suggesting that CYP450 and other nonkidney processes may also be impaired (29,30). Changes in bowel, hepatic, and kidney perfusion with critical illness may also alter drug absorption and disposition.

Ultimately, the high interpatient variability in pharmacokinetics with AKI is a significant challenge and complicates attempts to provide a generic approach to drug dosing. Because an increase in *Vd* is commonly noted, the initial dose should be increased if a prompt response is desired, particularly for hydrophilic antibiotics (*e.g.*, penicillins). These principles are summarized in Tables 2 and 3. More research is required to guide repeat dosing, especially for drugs that are subject to nonkidney clearance or those

Table 4. Important parameters that increase drug clearance with different kidney replacement therapies (31)

	Diffusive therapies (*e.g.*, HD)	Convective therapies (*e.g.*, HF)
Small solutes, *e.g.*, lithium	High Qb High Qd (ratio Qd:Qb >2.5) High-efficiency filter diffusion preferred over convection	High Qb and Quf Postfilter volume replacement High SA filter
Medium-sized solutes, *e.g.*, vancomycin	High Qb High flux filter High SA filter	High Qb and Quf Postfilter volume replacement High flux filter High SA filter Convection preferred over diffusion
Highly protein bound drugs, *e.g.*, sodium valproate (low clearance is anticipated)	High Qd High SA filter	High flux filter High SA filter Clearance possibly increased by prefilter volume replacement so convection may be preferred over diffusion

HD, hemodialysis; HF, hemofiltration; Qb, blood flow rate; Quf, ultrafiltration rate; Qd, dialysate flow rate; SA, surface area.

with a narrow therapeutic index, for which TDM is particularly useful.

Intermittent Hemodialysis

Drug clearance by kidney replacement therapies is additive to endogenous clearance (see Equation 2 in part 1 [2]), so it should be accounted for in determining the appropriate dosing regimen. Unfortunately, a complexity with doing so is that data concerning the effect of dialysis on drug clearance is often highly variable or simply not available. Limitations relate to advances in dialysis technology (data published decades ago are of questionable present-day relevance), the use of inadequate pharmacokinetic methods, or differences in the dialysis regimen used between published studies and local practice (blood and dialysate flow, filter size and type, *etc.*; Table 4) (31). In some cases, it may be possible to estimate drug clearance on the basis of the clearance of endogenous molecules, such as urea (a small molecule) or β2-microglobulin (a medium-sized molecule) from experimental studies.

Fortunately, it is possible to manage the effect of intermittent hemodialysis on the drug regimen by administering drugs relative to the timing of hemodialysis. Although high clearances are reported (even exceeding 200 ml/min, which far exceeds endogenous clearance of many drugs eliminated by the kidney), hemodialysis is of a relatively short duration. Therefore, the practical approach is to administer drugs that are cleared during dialysis after the dialysis treatment and to tolerate low concentrations during dialysis. If subtherapeutic concentrations during dialysis are not tolerated, then a small additional dose (calculated using Equation 1) can be given midway through dialysis. However, for patients where dialysis is removing uremic toxins that interfere with nonkidney clearance (see discussion in part 1 of this series [2]), there may be an increase in drug clearance soon after dialysis that is nonsustained during the interdialytic period. These principles are summarized in Tables 2 and 3.

One possible exception to this approach is the prescribing of aminoglycosides to patients with ESKD on intermittent hemodialysis, where a large dose can be administered immediately before dialysis to optimize the concentration–time profile (Figure 5).

Continuous KRT and Hybrid Techniques

Similar principles as outlined for intermittent hemodialysis can be applied to continuous KRT, noting that continuous KRT is applied for a longer duration. Unfortunately, there are minimal data regarding drug clearance during continuous KRT and much of it is limited to antibiotics. It is apparent (and predicted) that drug clearance by continuous KRT is less efficient than intermittent hemodialysis. However, the prolonged duration of continuous KRT means that it is more likely to remove a significant amount of the drug over the course of treatment. Reported continuous KRT clearances are quite variable given the heterogeneity of continuous KRT prescribing (blood, dialysate, and ultrafiltration rates; Table 4) and techniques used. This complicates the prediction of pharmacokinetics and individual drug dosing.

Depending on the technique used, the clearance rate of small water-soluble drugs with minimal protein binding by continuous KRT is approximately 20%–30% of that from intermittent modalities. Small-molecule clearance by continuous KRT appears to most strongly correlate with the effluent flow rate (32), which is the sum of dialysis fluid, replacement fluid, and net ultrafiltration rates (see Table 4). Changes in blood flow rates affect drug and solute clearance in convective continuous KRT to a greater extent than in diffusive therapies (33) (Table 4). The effect of hybrid techniques (*e.g.*, sustained low-efficiency dialysis or prolonged intermittent KRT) on pharmacokinetics is even less defined.

It is, therefore, difficult to make precise recommendations for the prescribing of most drugs during continuous KRT. Given that continuous KRT is generally prescribed to patients with AKI for which pharmacokinetic data are already uncertain, continuous KRT compounds the variability in drug clearance. Whether continuous KRT significantly increases the total clearance also depends on the

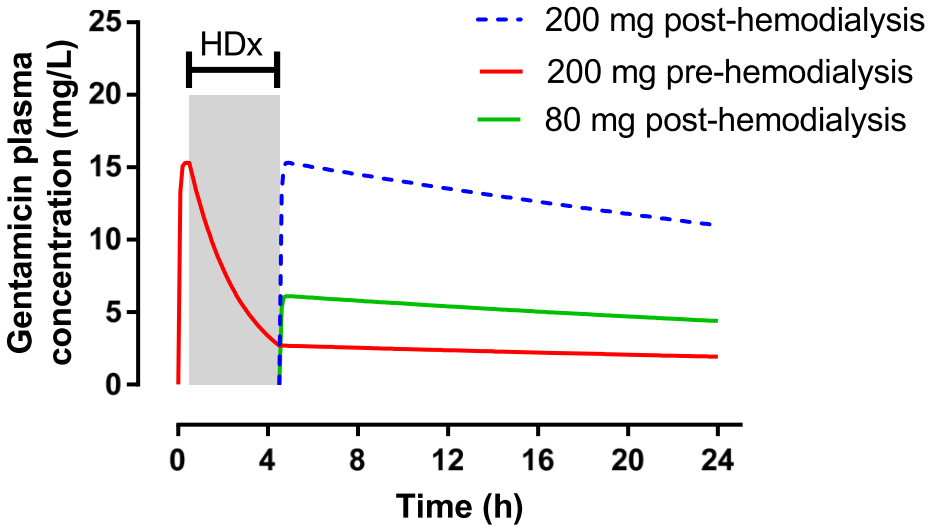

Figure 5. | The timing of gentamicin administration affects the concentration-time profile in patients using hemodialysis. Simulation on the basis of a 30-minute intravenous infusion of 200 or 80 mg gentamicin, using median values from Sowinski *et al.* (43) including *Vd* of 13.5 L, endogenous elimination $t_{1/2}$ of 39.4 hours, and elimination $t_{1/2}$ during hemodialysis (HDx) of 1.6 hours. Administration prehemodialysis maximizes the *C*max:MIC ratio (ratio of *C*max to the minimum inhibitory concentration of the bacteria; see part 1 [2]) and decreases the overall exposure. This demonstrates that a large dose can be administered immediately predialysis to take advantage of the concentration-dependent killing and postantibiotic effect of this antibiotic class. This maximizes the antibiotic concentration–time profile and drug effect, and the clearance achieved by dialysis allows for the aminoglycoside to be rapidly cleared to a less toxic concentration. Other antibiotics that also have a concentration-dependent killing and therefore may also benefit from a large dose immediately before dialysis are daptomycin (44) and the fluoroquinolones (45,46).

pharmacokinetics of the drugs of interest. For example, in patients with AKI receiving continuous hemodiafiltration, continuous KRT was more likely to significantly contribute to total clearance for vancomycin and meropenem, but less likely for ciprofloxacin and piperacillin (21). Given the lack of certainty, TDM remains the only reliable method of confirming attainment of target concentrations in this setting.

Peritoneal Dialysis

Similar principles as those outlined for continuous KRT apply to peritoneal dialysis (PD). Although there are different techniques with differing clearances and there are minimal data regarding drug clearance during PD, its overall additional effect on total clearance is probably low.

An important consideration is antibiotic dosing for PD-associated peritonitis, for which dosing recommendations are commonly made on the basis of uncontrolled observational studies using multiple antibiotics and without TDM (34). Further, some pharmacokinetic studies of intraperitoneal (IP) antibiotics were reported in patients without PD-associated peritonitis and did not report IP antibiotic concentrations or the effect of antibiotic-free PD exchanges. Therefore, it is not clear whether regimens made on the basis of these data achieve optimal antibiotic concentrations.

For example, until recently either cefalothin or cefazolin were the recommended first-line empirical antibiotics and were dosed identically (35), but it is now known that cefalothin is undetectable in IP fluid and plasma for at least 12 hours with once daily IP administration (36). This is because >30% of cefalothin clearance is by nonkidney metabolism, whereas cefazolin is predominantly cleared by the kidney. This is in contrast to vancomycin and gentamicin, where dosing is guided by plasma concentration monitoring (37). Therefore, comparing outcomes solely on the basis of the type of antibiotic (38), without considering dosing regimen, may be suboptimal.

TDM

The risk of sub- or supratherapeutic drug concentrations in clinical practice prompts the use of methods that confirm that the desired drug concentrations are achieved, such as TDM. Here, drug concentrations are measured in the patient and if the concentration is outside the desired therapeutic range, the dosing regimen is adjusted accordingly. Dosage adjustments may be iterative, but modifications can be improved with the above-discussed methods or computer-based approaches, including those using Bayesian methodology (39). TDM-based approaches overcome interindividual variation in pharmacokinetics and guide the delivery of individualized drug therapy. This tailored approach has advantages because much of the previously mentioned data were on the basis of population mean or median results, yet interindividual variability in results was often significant, particularly in critically ill patients.

TDM should be performed routinely for anti-infectives because the concentration is the key determinant of their effect (see part 1 of this series [2]). TDM is now an accepted standard of care and a key indicator for the appropriateness of antibiotic use and stewardship (40).

A complexity with TDM is ensuring that the appropriate plasma sample(s) are collected at the correct time. A limitation of TDM for many drugs is the slow turnaround time of assay results, such that drug concentrations are not available in a clinically useful time frame. Regardless, it is a

superior method of dosage adjustment and is also useful in research when exploring the dose-response relationship, particularly in the setting of altered physiology.

Future Research Directions

There are limited data to guide the prescribing of drugs in kidney impairment and widely used dosing recommendations are often made on the basis of outdated data and/or theoretical extrapolation.

Despite concerns regarding the effect of sub- and supratherapeutic drug concentrations, TDM and Bayesian-style computer-based dosing are not currently performed routinely for most drugs administered to patients receiving KRT. Furthermore, physiologically-based pharmacokinetic modeling is an approach that is increasingly used to predict the effect of changes in kidney function on pharmacokinetics and to guide rational drug dosing. Data obtained from routine TDM may help inform appropriate drug dosing in this understudied patient population. The lack of data for some drugs in some circumstances is so extreme that even a single case report, with proper sample collection and drug concentration measurements, would be informative.

The urgent need for further research is recognized by the FDA, who now recommend (although do not mandate) that pharmacokinetic studies are performed in patients with kidney disease for drugs that can be administered to patients with ESKD (41). For drugs already registered, smaller pilot studies can provide preliminary data to define the effect of kidney disease and dialysis on drug clearance and inform the design of future prospective studies. This will close the large gap in knowledge and ultimately assist in improving the drug prescribing and clinical outcomes in these vulnerable patients.

Conclusions

CKD and AKI are heterogeneous conditions with differing effects on pharmacokinetics, which complicates the development of generic drug dosing guidelines. Prescribing an appropriate initial dose and maintenance dosing regimen requires a rational approach and an understanding of the underlying pharmacokinetic concepts. Furthermore, the prescriber needs to be cognizant of dynamic factors that may change how a drug is handled over the treatment course.

TDM on the basis of drug concentrations can assist with optimization of the dosing regimen, supporting the achievement of personalized medicine, but requires the timely availability of drug concentrations and prescribers sufficiently trained in pharmacokinetic principles. An iterative approach accounts for potentially wide inter- and intraindividual variation in pharmacokinetic parameters and the careful use of TDM to monitor the chosen dosing regimen is essential.

The use of computer-based Bayesian approaches to dosing offers opportunities to tailor therapy and deliver personalized medical care; however, these are not widely used in routine clinical practice. Irrespective of how treatment is tailored to an individual patient, more pharmacokinetic data are required in all stages of CKD and AKI, including the effect of KRT, to inform drug dosing. The collection of this data are within the reach of most clinicians and hospital departments.

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Disclosures

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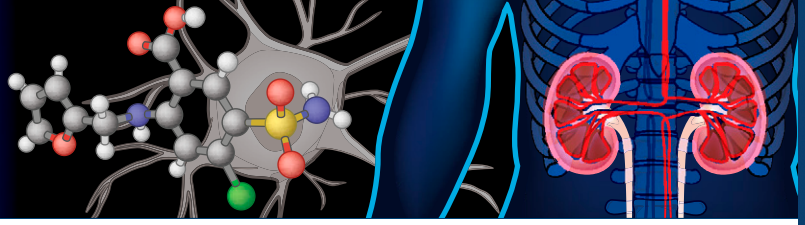

Clinical Pharmacodynamics

Principles of Drug Response and Alterations in Kidney Disease

Frieder Keller and Alexander Hann

Abstract

Pharmacokinetics and pharmacodynamics follow the logic of cause and consequence. Receptor-mediated and reversible effects can be distinguished from direct and irreversible effects. Reversible effects are capacity-limited and saturable whereas irreversible effects are limited only by the number of viable targets. In the case of receptor-mediated and reversible effects a threshold and a ceiling concentration can be defined. Antimicrobial drugs with concentration-dependent action are distinguished from drugs with time-dependent action. Concentration-dependent effects are associated with a high ceiling concentration and the target is the high peak. Time-dependent effects are associated with a high threshold concentration and the target is the high trough. During kidney dysfunction, alterations of drug response are usually attributed to pharmacokinetic but rarely to pharmacodynamic changes. Dose adjustment calculations, therefore, tacitly presume that pharmacodynamic parameters remain unchanged while only pharmacokinetic parameters are altered in kidney failure. Kidney dysfunction influences the pharmacokinetic parameters of at least 50% of all essential drugs. Clinicians usually consider pharmacokinetics when kidney disease is found, but pharmacodynamics is as important. Alterations of pharmacodynamic parameters are conceivable but only rarely reported in kidney failure. Sometimes surprising dosing adjustments are needed when pharmacodynamic concepts are brought into the decision process of which dose to choose. Pharmacokinetics and pharmacodynamics should both be considered when any dosing regimen is determined.

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Background and Introduction

Similar to the fact that every patient behaves differently, individual drugs also behave in different ways compared with each other. However, in nature and thus in medicine, basic laws can be identified that apply not only to every drug but also to every patient. Pharmacokinetics and pharmacodynamics present such mathematic laws (Figure 1). Drug concentrations produce the drug effects. Pharmacokinetics are the cause and pharmacodynamics the consequence. Pharmacokinetics allow us to calculate the dose adjustment in kidney disease where sometimes dramatic alterations can be found in roughly half the drugs. Pharmacodynamics allow for a quantitative description of the individual drug response. Additionally, they aid in modeling activation, inhibition, and interaction at the target receptor side (Table 1).

Two different mechanisms can be distinguished in pharmacodynamics. The reversible effects, which are usually receptor-mediated and saturable, and the irreversible effects, which are direct and proportional to rising concentrations. The reversible effects are observed with both increasing and decreasing concentrations. The irreversible effects, however, can only be produced by increasing concentrations.

In this paper, we will describe how pharmacodynamic parameters can be extracted from published data and subsequently how these parameters can be used to modify drug dosage in the state of kidney failure. As illustrated by apixaban with a reversible effect, the effect duration will last longer and can be predicted exactly from pharmacodynamic parameters when elimination is impaired in kidney failure. As an example with an irreversible effect, we will discuss how to make pharmacodynamics instrumental for carboplatin dose adjustment to kidney dysfunction. Further drugs will be discussed in the Supplemental Material where pharmacodynamics matter for medication in kidney patients.

Reversible Effect

Pharmacodynamics of reversible effects are capacity-limited and described by the saturable maximum effect (Emax) model (1). The effect cannot grow higher than the Emax, meaning that no more than a 100% response can be elicited due to the biologically limited number of molecular binding sites. An extension of the Emax model yields the sigmoid Hill equation (Supplemental Material). The Hill coefficient (H), sometimes referred to as the "γ" coefficient, represents a purely empiric parameter that determines the sigmoidicity of the effect-concentration correlation. The higher the H, the more the effect-concentration correlation looks S-shaped (Supplemental Figure 1). The usual

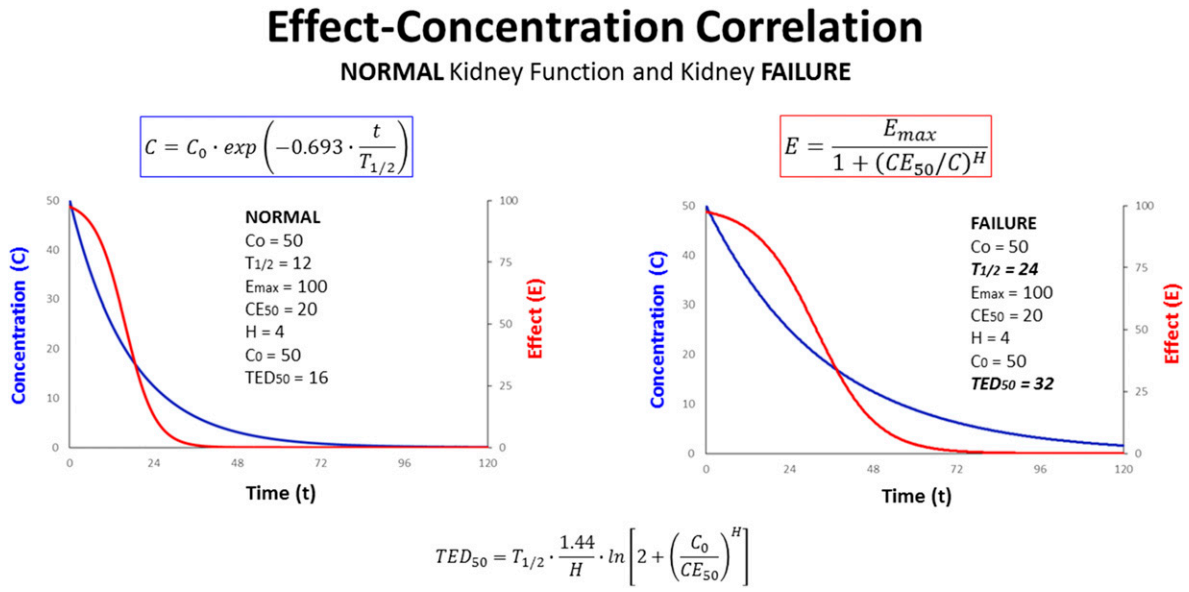

Figure 1. | **Pharmacodynamics (PD) follow pharmacokinetics (PK).** The time-dependent course of the effect can be modeled by inserting the time-dependent concentration decline (C) into the equation for the pharmacodynamic Emax model (E). In contrast to an irreversible effect, reversible effects (E) concomitantly diminish when concentrations (C) decline with time (t). The effect bisection time will rise in proportion to the $T_{1/2}$ ($T_{1/2}$→TED_{50}). This suggests to extend the administration interval when the elimination is impaired in kidney failure ($T_{1/2}$: 12→24). Emax, maximum effect; CE_{50}, concentration producing half-maximum effect; TED_{50}, effect bisection time.

form of the sigmoid Emax model can be rearranged into a true hyperbolic form.

$$E = \frac{E_{max}}{1 + \left(\frac{CE_{50}}{C}\right)^H}$$

Dividing by a fraction is done by multiplication with the reverse fraction: When neglecting the 1+ term in the denominator, one can immediately see that high concentrations (C) produce a strong effect (E). One can also see the effect of the concentration producing the half-maximum effect (CE_{50}). Because the CE_{50} corresponds to the K_d, a high CE_{50} is associated with only a weak effect (Supplemental Material). If the CE_{50} needed to produce 50% of Emax is low, however, the affinity to the receptor is high and this drug has a strong potency.

$$potency = \frac{1}{CE_{50}}$$

The Emax corresponds to the number of receptors or enzyme molecules. Thus, it is primarily a patient-related, not a drug-related, parameter. Emax can also explain how polypharmacy might work: in the case of synergistically acting drugs such as losartan and a thiazide, the receptor-mediated effects and thus the Emax values are additive on BP (E=Emax1+Emax2). Antagonistic combinations such as a typical antipsychotic with a dopaminergic anti-Parkinson drug are unfavorable because the Emax is mutually minimized (E=Emax1−Emax2).

On the other side, the CE_{50} parameter reflects the intrinsic power of the drug. It is a drug-related parameter. Alterations of the receptor affinity, however, result in CE_{50} changes and thus the individual response can be influenced by drug interaction, activation, or competition. Alterations of both Emax and CE_{50} can further occur as disease-related phenomena. In the elderly, changes in drug response often have been explained by an impaired kidney function. An increased sensitivity and a higher drug potency also can be due to a decrease in CE_{50} values in the elderly.

$$sensitivity = \frac{1}{CE_{50}}$$

An increased sensitivity has been reported for midazolam (CE_{50}: 522→223 ng/ml), nifedipine, morphine, phenytoin, and warfarin, but more resistance with a higher CE_{50}

Table 1. Pharmacodynamics of medications

Factors that influence the clinical pharmacologic drug response as measured by onset, intensity, and duration of effect. These factors act primarily by affecting the drug concentration at the receptor site
Drug dose
Drug pharmacokinetics
Receptor number
Organ response to receptor activation
Counter-regulatory (competing) influences at the receptor
Pathologic processes (aging, acute and chronic illness, and kidney disease) can affect pharmacodynamics (clinical response)
Decreased receptor number (Emax) and sensitivity (CE_{50})
Decreased receptor binding
Altered signal transduction
Drugs can interact and compete for similar receptors having multiple effects
Synergistic effects
Antagonistic effects
Drug toxicity (S-shaped effect-concentration correlation and Hill coefficient)

Emax, maximum effect; CE_{50}, concentration producing half-maximum effect.

has been observed for albuterol and metoprolol (2). In the former five examples, a dose reduction might be needed due to pharmacodynamic alterations. The opposite pharmacodynamic change is seen with albuterol and metoprolol that require a higher dose or a change to an alternative drug.

Furosemide and Canagliflozin

In contrast to tacit presumptions, a change in the CE_{50} can be predicted for furosemide and canagliflozin in CKD. Less potency and a decreased sensitivity with a higher CE_{50} will be predicted for furosemide or canagliflozin because a higher than normal dose with higher intratubular concentrations is needed to produce the diuretic effect: Although furosemide $T_{1/2}$ rises from 2 to 10 hours, nephrologists in general experienced that the dose should not be reduced, but instead be increased from 40 to >500 mg to obtain the diuretic effect in kidney failure (3). Canagliflozin, likewise, has been shown to require a higher dose of 300 mg in patients with kidney dysfunction because 100 mg results in underdosing, irrespective of the fact that the $T_{1/2}$ rises from 13 to 17 hours (4). The observations with furosemide and canagliflozin can be explained by pharmacodynamic not by pharmacokinetic changes in kidney failure.

The H is the exponent of a power function. A high H will result in an augmented CE_{50}/C ratio value if the ratio is >1.0 (>>1.0). In contrast, values of the CE_{50}/C ratio <1.0 will decrease dramatically (<<1.0). In the case of the special condition where the concentration, C, equals the CE_{50}, the ratio of CE_{50} over C is 1.0 with any H. Without knowing the H, therefore, the CE_{50} can be read off directly from simultaneous measurements of concentrations and corresponding effects (Figure 2).

$$1.0^{\pm H} = 1.0$$

Great progress has been made by distinguishing antimicrobial drugs with a concentration-dependent effect from drugs with a time-dependent effect. This difference can be explained by the H: Anti-infective drugs classified as concentration-dependent have a low H<2.0, whereas anti-infective drugs with a time-dependent effect have a high H>2.0 (5). Using the sigmoid Hill equation, the threshold (CE_{05}) and the ceiling concentration (CE_{95}) can be derived (Supplemental Material). For a high H, the CE_{95} will be low but, simultaneously, the CE_{05} is high (Supplemental Figure 1).

$$CE_{05} = 0.053^{\frac{1}{H}} \cdot CE_{50}$$

$$CE_{95} = 19^{\frac{1}{H}} \cdot CE_{50}$$

Drugs with a concentration-dependent effect and a low H have a high CE_{95}, such as gentamicin, levofloxacin, linezolide, daptomycin, colistin, and voriconazole (6). In this case a higher dose results in a stronger effect (Supplemental Figure 1). Conversely, drugs with a time-dependent effect and a high H have a low CE_{95}, but the CE_{05} will be high such as with piperacillin, ceftazidime, meropenem, vancomycin, clarithromycin, doxycycline, and antiviral drugs (6): In cases with a high threshold, low trough levels might miss the therapeutic target (Ctrough<CE_{05}), because they presumably could fall below the microbiologically minimal inhibitory concentration (MIC).

$$CE_{05} \cong MIC$$

The dosing regimen can be adjusted to the individual condition by changing either the dose or the length of the administration interval (τ). The decision depends on whether the peak or the trough is the target with repetitive dosing. A high peak is aimed at for the concentration-dependent pharmacodynamics (Ctarget=Cpeak) and a high trough for the time-dependent pharmacodynamics (Ctarget=Ctrough). To increase efficiency, drugs with a concentration-dependent action require the application of a higher dose (*e.g.*, apixaban). In contrast, drugs with a time-dependent action need a higher frequency of their dosing schedule, similar to a continuous infusion (*e.g.*, vancomycin).

Vancomycin, Meropenem, and Piperacillin

According to pharmacodynamically based regimens, vancomycin with a time-dependent action should be administered by continuous infusion to increase efficacy but decrease toxicity (7). The target concentration is no longer regarded as a trough level of 10 mg/L. Instead, the target is the average steady state serum concentration Css of up to 25 mg/L (Css×24 hours=area under the curve [AUC]) which is equivalent to an AUC of 400–600 hours×mg/L (7). To meet this target a bolus loading dose of 1500 mg (20 mg/kg) with a subsequently administered continuous infusion might be needed. The subsequent infusion rate must be adjusted to the kidney function or to the RRT according to pharmacokinetic principles. Analogous to vancomycin, meropenem should also be administered as a continuous infusion with the steady state concentration as the therapeutic target (Css) of four times the MIC and up to 32 mg/L (8). This target is in agreement with the time-dependent meropenem action because for H>2.0 the CE_{50} value roughly corresponds to four times the CE_{05} ($4 \times CE_{05} = CE_{50}$) and the CE_{05} relates to the MIC ($CE_{05} \sim MIC$). In agreement with these predictions, the mortality was less when β-lactam antibiotics were administered by prolonged infusion (>3 hours) versus short-term infusion (<60 minute); this difference was significant with meropenem and piperacillin but not with ceftazidime and not when just the $T_{1/2}$ values are prolonged due to impaired kidney function (9).

Apixaban

Pharmacokinetics and pharmacodynamics are closely correlated (Supplemental Material). When concentrations decrease with time, the reversible, receptor-mediated effect will also decrease with time (Figure 1). Analogous to the elimination $T_{1/2}$ in pharmacokinetics, the effect bisection time (TED_{50}) can be stated as a measure of the effect duration in pharmacodynamics (10). The TED_{50} indicates the time needed to decrease the effect by 50% (E2=0.50×E1); thus, the TED_{50} depends on the concentration (C1) producing the initial effect (E1).

$$TED_{50} = T_{1/2} \cdot \frac{1.44}{H} \cdot ln\left[2 + \left(\frac{C_1}{CE_{50}}\right)^H\right]$$

The pharmacokinetics of apixaban and rivaroxaban are comparable regarding their normal $T_{1/2}$ of 8 hours for both

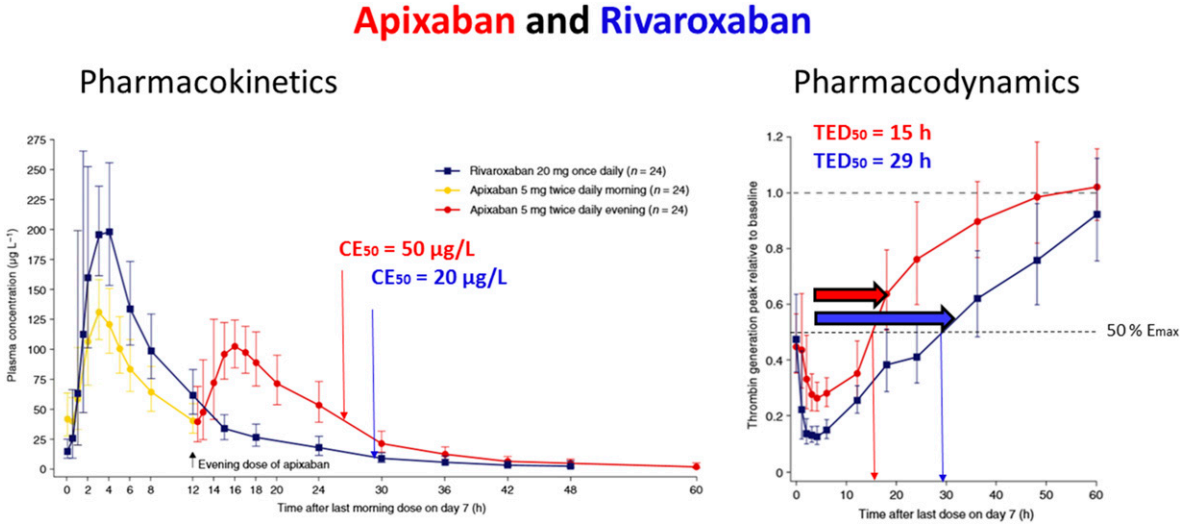

Figure 2. | **Pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban** (12)**.** Pharmacodynamics (right): The effect bisection time (TED_{50}) can be read off at approximately 15 hours for apixaban (red arrow) and at 29 hours for rivaroxaban (blue arrow). The time after dosing when 50% of maximum effect (Emax) is produced is 15 hours with apixaban but 29 hours with rivaroxaban. Pharmacokinetics (left): At 27 hours (=12+15), the concentration producing 50% of Emax (CE_{50}) can visually be determined with CE_{50}=50 μg/L for apixaban (red) but at 29 hours with CE_{50}=20 μg/L for rivaroxaban (blue).

direct-acting oral anticoagulants (11). However, the recommended administration interval differs with 12 hours for apixaban and 24 hours for rivaroxaban. It has been demonstrated that plasma levels after a regular dose of 5 mg apixaban reach a maximum concentration of 139 μg/L, in comparison with 20 mg rivaroxaban reaching a higher maximum plasma concentration of 227 μg/L (12). From the published diagram depicting the effect on thrombin generation, the TED_{50} can be read off with TED_{50}=15 hours for apixaban and with TED_{50}=29 hours for rivaroxaban (Figure 2). In addition, the concentration producing the CE_{50} can visually be determined with CE_{50}=50 μg/L for apixaban and with CE_{50}=20 μg/L for rivaroxaban just at the time where 50% of the maximum effect is produced (Figure 2).

Using the equation for the TED_{50} and on the basis of these pharmacokinetic and pharmacodynamic parameter values, the H can be estimated by an iterative numeric solution (Supplemental Figure 2). Thus, the still missing pharmacodynamic parameter can be derived and the estimates are quite comparable with H=1.4 for apixaban and H=1.2 for rivaroxaban. Accordingly, the pharmacodynamics of both apixaban and rivaroxaban can be stated to be concentration-dependent, allowing for a long administration interval. Such inferences can explain why rivaroxaban is applied with an administration interval of 24 hours, although its $T_{1/2}$ is only 8 hours.

The insight into the pharmacodynamics might affect clinical dosing practice in kidney failure where the $T_{1/2}$ of apixaban rises to 17 hours, whereas the rivaroxaban $T_{1/2}$ increases to only 10 hours (11). The antithrombotic efficacy and the bleeding risk were not different for apixaban and rivaroxaban even in CKD (13). The recommended dose of apixaban is 2.5 mg twice a day in advanced kidney disease (13). With 2.5 mg apixaban twice a day the trough concentrations were measured as low as 50 μg/L (14). Because the $T_{1/2}$ is 17 hours, the corresponding peak concentration will be estimated with 82 μg/L. Because apixaban has a concentration-dependent effect, the aim should be the normal peak of 139 μg/L.

Instead of dosing 2.5 mg every 12 hours, the pharmacodynamic dose adjustment of apixaban to kidney failure would suggest 5 mg once a day because the $T_{1/2}$ is 17 hours and the TED_{50} will be estimated with TED_{50}=29 hours. Thus, the suggested apixaban administration interval is just equal to the 24-hour interval of rivaroxaban in kidney failure not requiring dialysis. Otherwise, the trend for apixaban underdosing becomes apparent when the dose for patients receiving dialysis is recommended as 5 mg twice daily, whereas rivaroxaban could still be dosed at 15 mg once a day (13).

Anticancer Therapy

In pharmacokinetics the drug dose results in one concentration but in pharmacodynamics one and the same concentration results in at least two effects—the beneficial and the adverse effect (Supplemental Figure 3). Conventional drugs with a beneficial effect will also have adverse effects. The adverse drug reaction can even be used for a pharmacodynamic monitoring of the therapeutic effect. The therapeutic response to the tyrosine kinase inhibitor erlotinib, likewise, can only be expected if there is a skin rash. Mild myelosuppression—not myelotoxicity, not aplasia—but still tolerable grade 3 anemia, thrombocytopenia, neutropenia, or lymphocytopenia are easy measurable drug effects that might indicate sufficiently high dosing to guarantee the therapeutic target in oncology and immunosuppression (Table 2). Therefore, a grade 3 neutropenia should not give reason to reduce the dose: Some toxicity is needed for anticancer chemotherapy to meet the therapeutic target.

Furosemide Infusion

Ototoxicity is considered to be a serious side effect of furosemide. This side effect must be classified as

Table 2. Adverse drug events as surrogate markers for the pharmacodynamic monitoring of therapeutic targets

Class	Drug	Pharmacodynamic Target	Reference
Anticancer	Adriamycin=doxorubicin	Neutrophil count 1.5/nl	(27)
	Carboplatin	Grade 2 and 3 neutropenia 1.5–1.0/nl	(28)
	Cisplatin	Neutrophil count 1.5/nl	(27)
	Cyclophosphamide	Neutrophil count 1.5/nl	(27)
	Docetaxel	Grade 3–4 neutropenia <1.0/nl	(29)
	Doxorubicin	Neutrophil count 1.5/nl	(27)
	Fluorouracil (5FU)	Neutrophil count 1.5/nl	(27)
	Paclitaxel escalated	Grade 2–3 neutropenia 1.0–1.5/nl	(30)
Anti-infective	Celgosivir	Δ platelet nadir −Δ 60/nl Δ hematocrit −Δ 6%	(31)
	Valganciclovir	White blood cell count <3/nl	(32)
Hematology	Imatinib	White blood cell count <4.0/nl	(33)
	Lenalidomide	Δ platelet −Δ 50% Grade 3–4 neutropenia and thrombocytopenia	(34)
	Trifluridine/tipiracil	Neutropenia or leukopenia or anemia or thrombocytopenia grade 3–4	(35)
Immunosuppression	Azathioprine	White blood cell count <3.0/nl Neutropenia <1.0/nl Thrombocytopenia <100/nl	(36)
	Cyclophosphamide	Neutrophil count <4/nl, White blood cell count <4/nl, Lymphopenia threshold 1.0/nl	(37) (38) (39)
	Mycophenolate	Leukopenia <4/nl	(40)
	Rituximab	CD19+ B cells <10/mm^3=10/μl=0.010/nl CD4+ T cells <200/μl=0.2/nl	(22) (41–50)

Mild myelosuppression with anemia, neutropenia, lymphocytopenia, and thrombocytopenia might indicate a sufficiently high dose of anticancer, anti-infective, or hematologic and immunosuppressive drugs.

concentration-dependent because the H for the hearing loss under furosemide is reportedly low at H=1.5 (15). Accordingly, the occurrence of ototoxicity is less likely when furosemide is administered by a continuous infusion instead of bolus injection, the latter resulting in a high serum peak level. High serum peak levels and ototoxicity will be avoided by a continuous infusion. Continuous infusion also has been shown to increase the diuretic response and will be advantageous regarding the higher dosage of furosemide usually needed in kidney failure (16).

Irreversible Effect

In contrast to the reversible effects, irreversible effects rarely have been modeled in the literature. Published examples for irreversible effects include the drugs ibrutinib (17), cisplatin (18), clopidogrel (19), and pantoprazole (20). An irreversible effect might be produced by one single drug administration. Irreversible effects persist much longer than concentrations of the drug will remain measurable in the body (Supplemental Material). Whereas reversible effects target a receptor or enzyme molecule, irreversible effects target an on-off mechanism or an active cell (bacteria, cancer cell, immune cell).

Rituximab

The normal dose of the CD20+ B cell antibody rituximab is 375 mg/sqm weekly for 4 weeks. However, two doses of 1000 mg within 2 weeks became the preferred regimen published in the Membranous Nephropathy Trial of Rituximab on the nephrotic syndrome due to membranous GN (21). Although shorter and less frequently dosed (time of treatment [T]=2 weeks), this protocol produces a long-lasting effect as does the standard 4 weeks regimen (21). The irreversible effect can be modeled as depending on dose (D), volume (Vd), and the time of infusion (4 hours) but also as depending on the T.

$$E_{irrev} = \frac{D}{Vd} \cdot exp\left(-0.693 \cdot \frac{T}{T_{1/2}}\right)$$

As quantitated here for the irreversible effect, the total D (D) (2×1000 mg=2000 mg) given within a shorter time of 2 weeks (T=14 days) will induce a 2.3-fold stronger response (E irrev) than the same dose (4×500 mg=2000 mg) given within the usual 4 weeks (T=28 days). With $T_{1/2}$=11.5 days, rituximab concentrations are negligible after 50 days but the effect on B cells will persist for 200 days or even up to 500 days (22). Thus, the effect on the initial B cell population can be stated as irreversible. The irreversible effect will persist until the bone marrow regenerates and the immune system will be able to produce a new B cell generation.

Carboplatin

Pharmacodynamics of an irreversible effect will have considerable implications for drug dose adjustment in kidney failure. The difference between reversible and irreversible effects can be illustrated with carboplatin, where the $T_{1/2}$ increases four-fold from 4.5 to 17 hours in kidney failure (23). With the traditional Calvert formula, the pharmacodynamics of a reversible effect are presumed and the area under the curve is kept unchanged when the kidney function changes (AUC=constant [const.]). With the target AUC of 7 minutes×mg/ml the normal dose of 1000 mg would have to

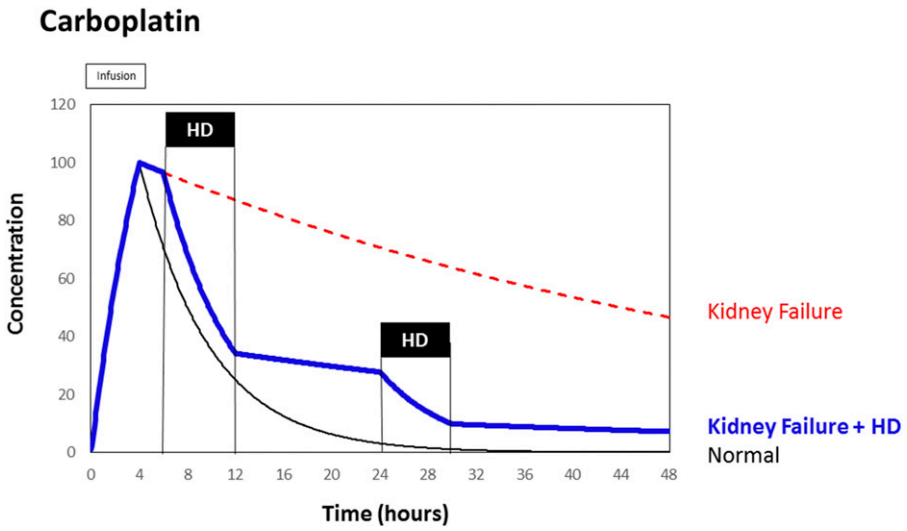

Figure 3. | Carboplatin and kidney failure: Near-normal elimination kinetics can be established by hemodialysis (HD) initiated 2 hours after carboplatin infusion.

be reduced to 210 mg for kidney failure with a GFR of 5 ml/min (24) when using the Calvert equation (210=7×[5+25]).

$$D = AUC \cdot [GFR + 25]$$

In the case of kidney failure, however, a less rigorous dose reduction is required than proportionate to the rise of the $T_{1/2}$ because only the higher dose can here produce the same irreversible effect as with normal conditions (E irrev=const.): Conveniently, the recommended time of infusion is unchanged with T=2 hours (25). When keeping the infusion time const. (T=Tnorm=const.), the carboplatin dose must be reduced (Supplemental Material).

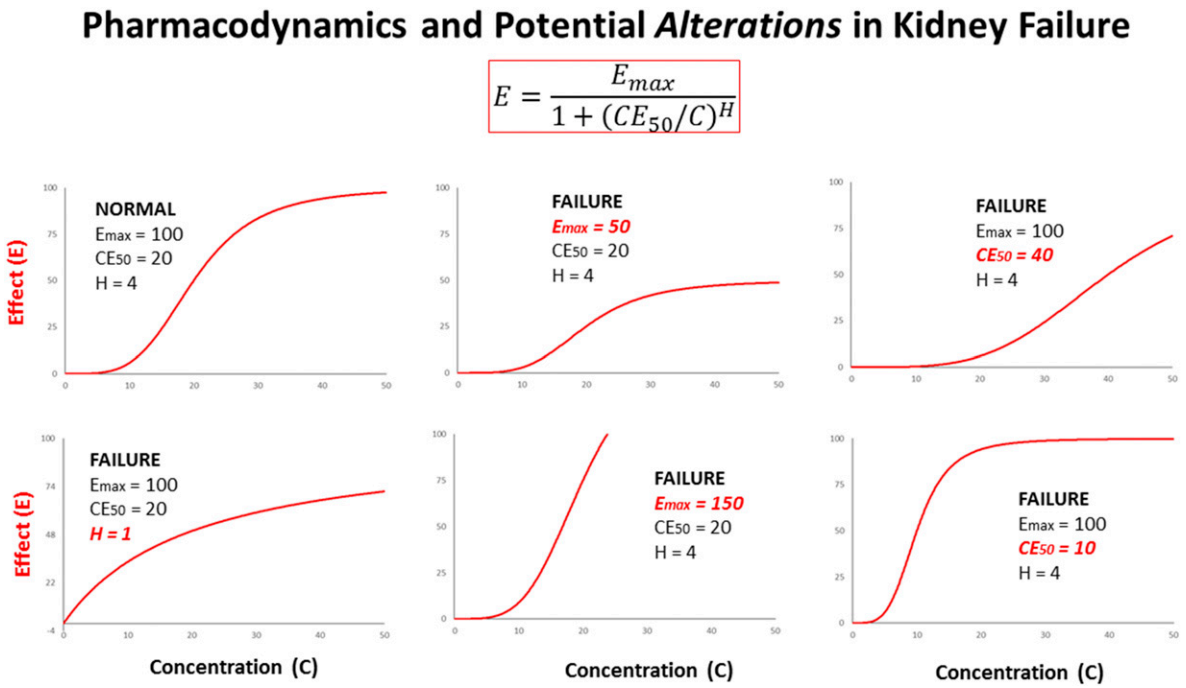

Figure 4. | The effect (E) depends on concentrations (C) according to the sigmoid Emax model. Pharmacodynamic parameters as determined for normal kidney function potentially might change due to kidney failure: When the Hill coefficient decreases (H: →1.0) the dose must be increased. When the maximum effect is diminished (Emax: →50) more of the drug or another drug should be given. When the effects of two drugs are additive (Emax: →150) the combination has advantages. When the concentration producing the half-maximum effect increases (CE_{50}: →40) a higher dose will be needed. Conversely, when the sensitivity increases (CE_{50}: →10) the dose must be reduced. Most frequently, but not exclusively so, the dosage should be reduced in kidney failure.

$$D = D_{norm} \cdot exp\left(0.693 \cdot \frac{T}{T_{1/2}} - 0.693 \cdot \frac{T_{norm}}{T_{1/2norm}}\right)$$

But the dose adjustment on the basis of the pharmacodynamics of an irreversible effect suggests that a dose of 770 mg not 210 mg will be needed to stop the cancer cells: Thus the normal standard dose will be reduced by 23% when giving the 770 mg (1.0–770/1000=0.23) but not by 79% as when reducing to 210 mg (1.0–210/1000=0.79). To limit the risk for severe and intolerable adverse events it will be necessary and has frequently been recommended to perform an immediate hemodialysis session just 2 hours after carboplatin administration (23,25,26). The hemodialysis can be seen as an artificial substitute of normal kidney function (Figure 3).

No dose reduction would be needed if the infusion time could be extended in parallel with the four-fold prolongation in the elimination $T_{1/2}$. But such a four-times-longer infusion time (T=8 hours) would be unfeasible with carboplatin in clinical practice and this regimen does not solve the problem of an increased risk for toxicity due to a rise in the AUC.

Conclusions

Values for pharmacodynamic parameters can be extracted from the published literature using respective key words. With the keywords "EC50+pharmacodynamics" a total of 16,051 publications, with "Hill+pharmacodynamics" 2412 publications, with "E-max model+pharmacodynamics" 436 publications, and even for the keywords "CE_{50}+pharmacodynamics" a total of 41 publications can be identified in PubMed (December 2017). In kidney failure, pharmacokinetics can dramatically change leading to alterations in drug action; but alterations in pharmacodynamic parameters have rarely been considered (Figure 4). Sometimes the values for the CE_{50} concentration and the H can be extracted and exploited to derive dose modifications appropriate for target attainment. The target is the peak level close to the CE_{95} for a life-saving induction therapy. The target is the trough level above the CE_{05} with a long-term maintenance therapy. However, for irreversible effects the target should be the normal maximum concentration.

Disclosures

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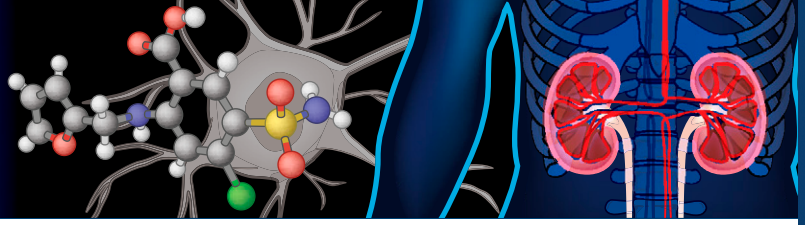

Clinical Pharmacogenomics
Applications in Nephrology

Solomon M. Adams,[1] *Karryn R. Crisamore*,[1] *and Philip E. Empey*[2,3]

Abstract

Pharmacogenomics is a tool for practitioners to provide precision pharmacotherapy using genomics. All providers are likely to encounter genomic data in practice with the expectation that they are able to successfully apply it to patient care. Pharmacogenomics tests for genetic variations in genes that are responsible for drug metabolism, transport, and targets of drug action. Variations can increase the risk for drug toxicity or poor efficacy. Pharmacogenomics can, therefore, be used to help select the best medication or aid in dosing. Nephrologists routinely treat cardiovascular disease and manage patients after kidney transplantation, two situations for which there are several high-evidence clinical recommendations for commonly used anticoagulants, antiplatelets, statins, and transplant medications. Successful use of pharmacogenomics in practice requires that providers are familiar with how to access and use pharmacogenomics resources. Similarly, clinical decision making related to whether to use existing data, whether to order testing, and if data should be used in practice is needed to deliver precision medicine. Pharmacogenomics is applicable to virtually every medical specialty, and nephrologists are well positioned to be implementation leaders.

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Introduction

Few medical interventions are as accessible to the clinician as pharmacotherapy. However, interpatient variability in drug pharmacokinetics (absorption, metabolism, distribution, and elimination) and pharmacodynamics (concentration-effect relationships) challenges drug selection and dosing (1). Precision medicine, driven by advances in genomics technology, promises a means to mitigate these unpredictable medication responses. Nephrologists have been champions of the use of biomarkers to tailor medication dosing for decades with their use of measurements, like creatinine clearance, to estimate kidney function (2). Combined with other measures, such as weight, age, and population-based nomograms, most nephrologists are already using precision medicine routinely in daily practice.

Despite efforts to incorporate tailored dosing, an estimated 2.2 million adverse drug reactions occur in the United States annually, and medication efficacy rates vary considerably (3). Difficulty in predicting medication response has led to the paradigm of frequent dose titration and iteration among medications. Collectively, these place a significant burden on the patient, the provider, and the health care system. One potential solution is the use of individual genomic data to guide prescribing, which is termed pharmacogenomics (4).

Rather than a one size fits all dosing, pharmacogenomics may enable *a priori* identification of which patients are likely to experience therapeutic failure or toxicity, leading to individualized pharmacotherapy (Figure 1). The past two decades have yielded a rapid influx of genomic data, with over 20,000 new pharmacogenomics citations in PubMed, in excess of 3500 gene-drug variant associations reported, and nearly 200 medications with pharmacogenomics information in their Food and Drug Administration (FDA)–approved drug product labeling (5,6). Common genetic variations predict activity of drug-metabolizing enzymes, drug affinity for treatment targets, and risk for immune reaction to medications among others (7,8). Furthermore, a number of medical centers have implemented clinical pharmacogenomics services and are providing new solutions to complement biometric-based dosing and clinician judgement to deliver more precision prescribing (9). As this area has grown, pharmacogenomics has transitioned from single gene/variant and drug response associations (originally coined as "pharmacogenetics") to a broader analysis of multiple genetic variants from many genes and environmental factors to personalize medication therapy (10). Figure 2 describes the growth and transition of pharmacogenomics over the past 38 years.

In this review, we provide an overview of the clinical use of pharmacogenomics, focusing on specific medications highly relevant to the nephrologist. The scientific basis for pharmacogenomics, decision-making processes for using pharmacogenomics in practice, and clinician-friendly pharmacogenomics resources will be presented. Finally, we will discuss the current state of pharmacogenomics research to highlight emerging concepts.

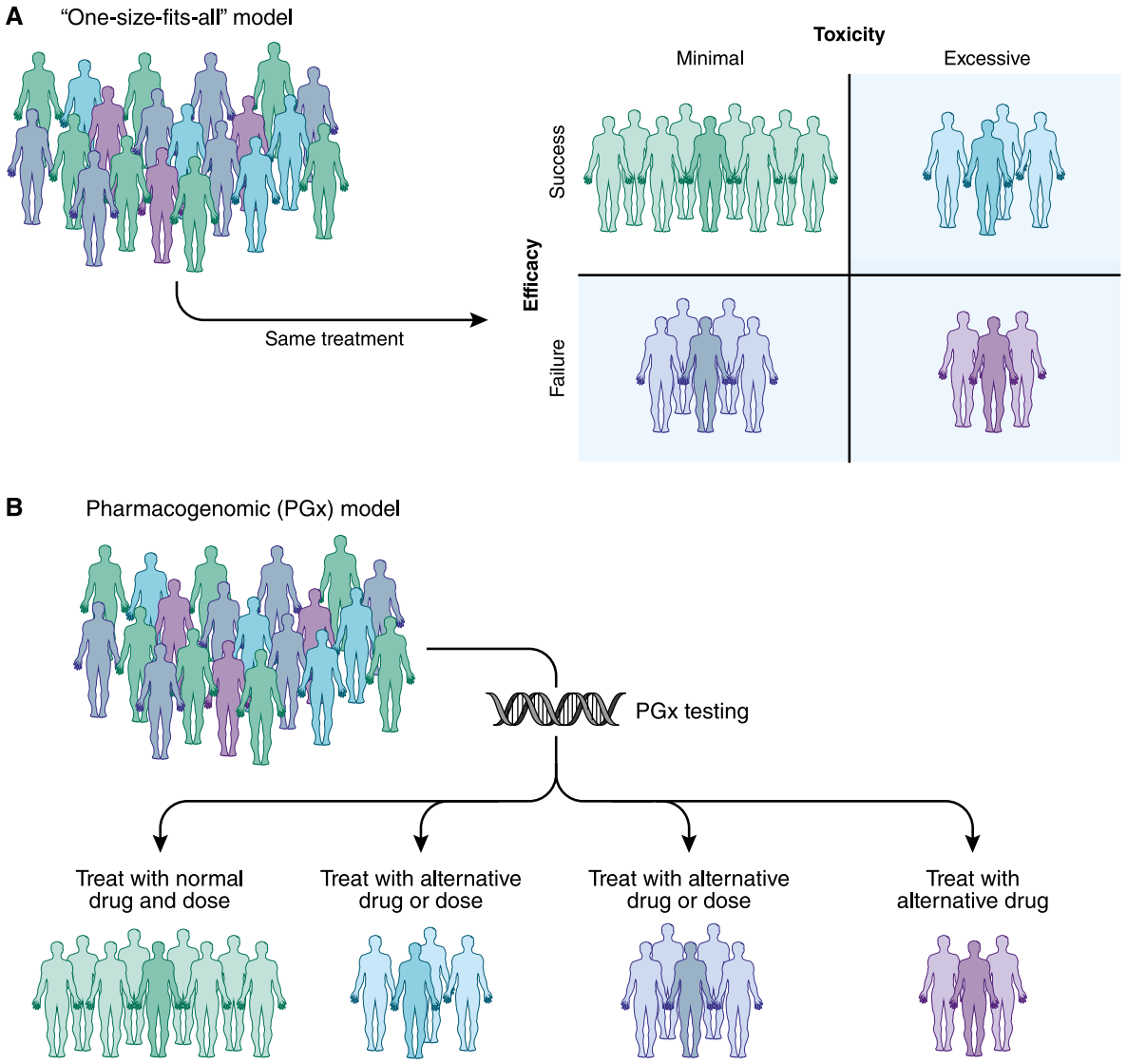

Figure 1. | Individualized therapy through pharmacogenomics may predict patients who should receive a different dose or alternative medication. (A) Shows how a conventional one size fits all dosing model may lead to patients with therapeutic failure, drug toxicity, or both (purple shaded). (B) In contrast, shows that a pharmacogenomics-guided dosing model may allow prediction of more appropriate dose or drug alternatives.

Science of Pharmacogenomics as a Driver of Medication Response Variability

Consider the following patient who illustrates the potential of pharmacogenomics. J.H., a 60-year-old black man with a history of ESKD, received a kidney transplant last month. He was started on 0.2 mg/kg per day tacrolimus, and over the past 2 weeks in the hospital, he has been titrated up to 0.6 mg/kg per day; however, his most recent tacrolimus trough level is subtherapeutic at 2 ng/ml. Today, he has severe flank pain and is showing signs of severe acute rejection. Ultimately, J.H. suffers from allograft loss and is reinitiated on hemodialysis. The monthly quality improvement meeting concludes that his acute rejection may have been averted with more aggressive immunosuppression and possibly, a higher tacrolimus starting dose but that the titration was in line with best practice. Nothing that was known of J.H. indicated that he would need an increased dose of tacrolimus to obtain therapeutic concentrations, but you wonder if there is a method for predicting patients, like J.H., *a priori*.

Humans carry 23 pairs of chromosomes inherited from the maternal and paternal lineage to make up the genome. With the exception of sex chromosomes, we, therefore, have two copies of every gene. An allele refers to a single or multiple nucleotides on a single chromosome, which may be notated as the actual nucleotide (*i.e.*, ATCG) or as an abstracted representation of the nucleotide(s) (*e.g.*, star alleles). If at a given genomic position, two alleles are the same, then the person would be homozygous at that particular position, and if the alleles are different, they are heterozygous. Like many patients of African ancestry, J.H. carried a single-nucleotide polymorphism (SNP), a single-nucleotide base change, on both copies at marker rs776746 on his seventh chromosome. At this position, about 90% of whites

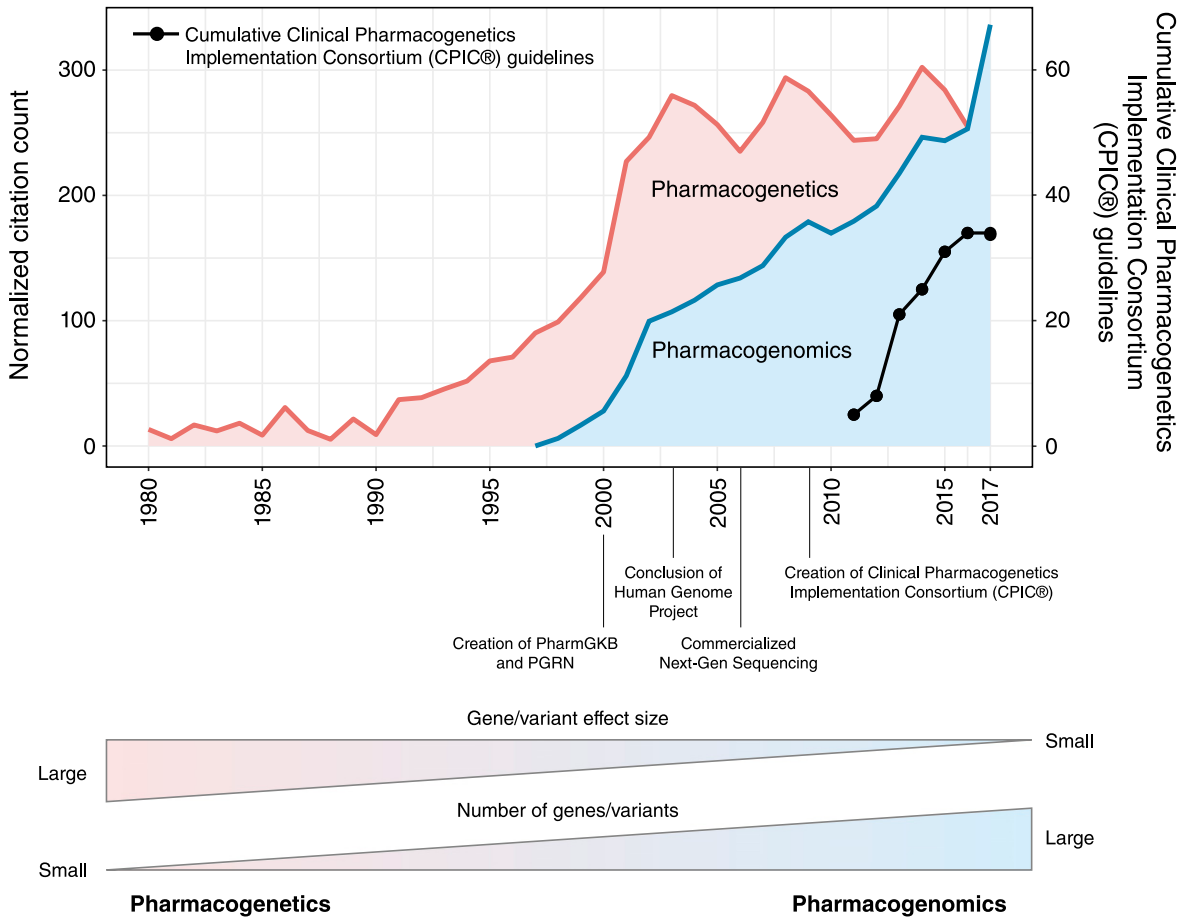

Figure 2. | The rise of pharmacogenomics is evident from the growth in genomic technology and the use of multiple genes and variants to understand drug response. Numbers of citations indexed in PubMed that contain the words "pharmacogenetics" (red) and "pharmacogenomics" (blue), excluding review papers, and normalized to the average number of total yearly citations in PubMed. The black line shows the cumulative number of published guidelines by the Clinical Pharmacogenetics Implementation Consortium (CPIC). These show the perspective change from studying the effect of a single gene variant with a large effect size on drug response (pharmacogenetics) to the effect of many genetic variants on many drugs (pharmacogenomics). This transition from the "etic" to "omic" terminology that began in the late 1990s signaled the beginning of precision medicine with pharmacogenomics. PGRN, Pharmacogenomics Research Network; PharmGKB, Pharmacogenomics Knowledge Base.

have a cytosine on both chromosomes (two "C" alleles, the "C/C" genotype, termed *CYP3A5* *3/*3), whereas nearly 50% of individuals with African ancestry carry thiamine on both chromosomes (two "T" alleles, "T/T" genotype, termed *CYP3A5* *1/*1) (11). From this star alleles nomenclature, we can predict a clinically useful phenotype, which results from interactions between the genotype and the environment. For example, a person with *CYP3A5* *3/*3 does not express the CYP3A5 protein and is thus called a "poor metabolizer," whereas a person with *CYP3A5* *1/*1 alleles does express the CYP3A5 protein and is called a "normal metabolizer." In the case of both (*e.g.*, *CYP3A5* *1/*3), the person has an intermediate phenotype and is called an "intermediate metabolizer" (12). For reference, a list of commonly used pharmacogenomics alleles in this paper and their corresponding genetic variations are included in Table 1.

CYP3A5 is a member of the cytochrome p-450 enzyme system. It catalyzes the oxidation of tacrolimus to inactive metabolites (12). Patients who express CYP3A5 tend to require higher than usual tacrolimus doses to reach therapeutic concentrations (13). If J.H.'s CYP3A5 status was known at the initiation of therapy, then a more informed decision about tacrolimus dosing could be made. Knowing basic genetic information requires that clinicians recognize individual variability early in clinical care. This point is further illustrated in Figure 3, showing how unrecognized subpopulations may be unmasked by pharmacogenomics. In this situation, the theoretical median dose requirements may vary widely between these subpopulations and the ungenotyped aggregate.

Pharmacogenomics Resources

Easily accessible web resources are available to the clinician to help interpret pharmacogenomics information. These include data aggregation sites, evidence-based clinical guidelines, and regulatory data (14). Pharmacogenomics information may be found in the FDA-approved prescribing information, although these data may appear in different sections (*e.g.*, dosing information, clinical pharmacology, *etc.*) (6). The Pharmacogenomics Knowledge Base (www.pharmgkb.org/) is a comprehensive

Table 1. Selected gene alleles, their causative variations, and associated phenotypes

Gene and Allele	Causative Variation(s)	Phenotype
CYP2C9		
*2	rs1799853 (T)	Decreased function
*3	rs1057910 (C)	Decreased function
CYP4F2		
*3	rs2108622 (T)	Decreased function
CYP3A5		
*3	rs776746 (C)	Decreased function
CYP2C19		
*2	rs4244285 (A)	Decreased function
*3	rs4986893 (A)	Decreased function
*17	rs12248560 (T)	Increased function
TPMT		
*2	rs1800462 (G)	Decreased function
*3A	rs1800460 (T); rs1142345 (C)	Decreased function
*3B	rs1800460 (T)	Decreased function
*3C	rs1142345 (C)	Decreased function
*4	rs1800584 (T)	Decreased function
VKORC1		
−1639G>A	rs9923231 (T)	Increased sensitivity to warfarin
SLCO1B1		
*5	rs4149056 (C)	Decreased function
HLA-B		
*58:01	N/A	Increased SCAR risk

TPMT, thiopurine methyltransferase; N/A, not applicable; SCAR, severe cutaneous adverse reaction.

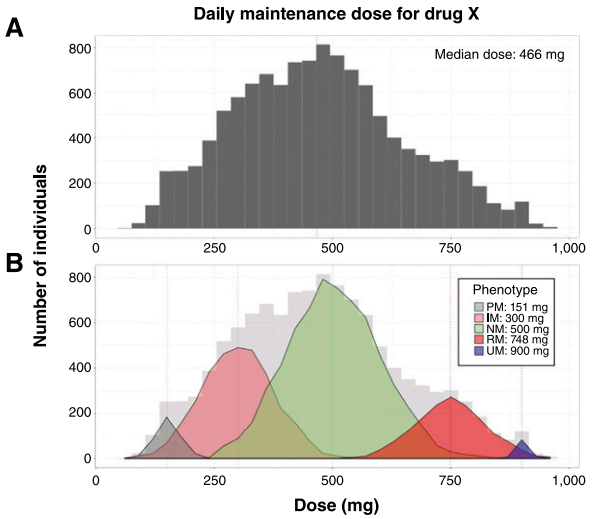

Figure 3. | Simulated dosing data for drug X after patient titration to effect shows distinct subpopulations based on genetics. A shows the distribution of total daily dose among the aggregate population, suggesting a mostly normal distribution of doses. B shows population substructure on the basis of genetic variants in the gene responsible for metabolism of drug X for poor metabolizers (PMs), intermediate metabolizers (IMs), normal metabolizers (NMs), rapid metabolizers (RMs), and ultrapid metabolizers (UMs). Patients with decreased metabolism of drug X (PMs and IMs) have a lower effective dose, whereas patients with increased metabolism (RMs and UMs) require higher doses. This shows the utility of pharmacogenomics-based dosing in addition to clinical factors to identify subpopulations.

annotated pharmacogenomics resource that includes clinical guidelines, FDA labeling, and pharmacogenomics-related pathways (5). Organizations that compile pharmacogenomics evidence to develop clinical guidelines include the Clinical Pharmacogenetics Implementation Consortium (CPIC; www.cpicpgx.org) and the Dutch Pharmacogenetics Working Group (15). The CPIC was created to overcome implementation barriers by developing standardized clinical pharmacogenomics guidelines. Over 20 guidelines have been published since 2012, and they are publicly available to aid clinicians in translating genetic laboratory test results into actionable prescribing decisions (16).

Clinical Pharmacogenomics for the Nephrologist

In the following sections, drug-gene pairs with clinical guidelines and a high level of evidence in conditions commonly treated by the nephrologist are presented. The focus is on cardiovascular disease and transplantation versus an exhaustive list of drugs and genes. Readers are encouraged to investigate the primary literature described herein as a means to further learn about pharmacogenomics in relevant therapeutic areas. A summary of the gene-drug pairs and clinical guidelines discussed is provided in Table 2.

Cardiovascular Disease

Cardiovascular disease is a leading cause of death for patients suffering from CKD. Hallmarks of cardiovascular disease secondary to CKD are cardiac remodeling, atherosclerosis, and arteriosclerosis (17). Pharmacogenomics of cardiovascular disease is an active area of research and clinical implementation, with evidence-based guidelines for antiplatelets, anticoagulation, and hyperlipidemia (16,18,19).

Antiplatelet Agents and Anticoagulants

Warfarin. Warfarin is a vitamin K antagonist that inhibits coagulation by inhibiting the formation of coagulation factors II, VII, IX, and X and proteins C and S (20). It is a narrow therapeutic index drug with high interpatient variability and a delayed time to action (*i.e.*, dose changes are not reflected in laboratory values for approximately 72 hours) (21). Frequent monitoring of the international normalized ratio (INR) over days to weeks is needed to determine the right dose. Patients with impaired kidney function are further known to require lower dosages of warfarin, have worse control of anticoagulation, and are at a higher risk for major hemorrhage (22).

Warfarin pharmacokinetics and pharmacodynamics are affected by multiple genotypes. Genetic variations affecting CYP2C9 and CYP4F2 metabolism and VKORC1 sensitivity are known to predict the dose needed to attain optimal anticoagulation (a therapeutic INR) but are not without controversy (23). In 2013, divergent clinical trial results significantly diminished enthusiasm for routine warfarin pharmacogenomics in all patients. Although the European Pharmacogenetics of Anticoagulation Therapy Study showed that use of a pharmacogenomics algorithm

Table 2. Summary of the gene-drug pairs and clinical guidelines relevant to nephrology

Drug	Gene	Clinical Guidance Summary	Ref.
Warfarin	*CYP2C9*	Use lower dose if a poor or intermediate metabolizer (*e.g.*, *2/*2, *1/*2)	23
Warfarin	*CYP4F2*	Use lower dose if decreased activity (*3)	23
Warfarin	*VKORC1*	Use lower dose if increased sensitivity (−1639G>A)	23
Clopidogrel	*CYP2C19*	Use alternative antiplatelet agent if poor or intermediate metabolizer (*e.g.*, *2/*2, *1/*2); monitor for bleeding if ultrarapid metabolizer (*1/*17, *17/*17)	35
Simvastatin	*SLCO1B1*	Use lower dose or alternative agent in patients with decreased transporter activity (*5, *15, *17)	37
Azathioprine	*TPMT*	Patients with decreased TPMT function have higher risk for toxicity	39
Tacrolimus	*CYP3A5*	Carriers of at least one functional (*1) allele may require higher doses	13
Voriconazole	*CYP2C19*	Use an alternative agent in CYP2C19 rapid/ultrarapid metabolizer (*1/*17, *17/*17); use alternative agent or lower dose in CYP2C19 poor metabolizer (*2/*2, *3/*3)	40
Allopurinol	*HLA-B*	User an alternative uric acid–lowering agent in patients who carry at least one *58:01 allele	53

TPMT, thiopurine methyltransferase.

increased time in therapeutic range versus fixed dosing at 12 weeks in a predominantly white population, the Clarification of Optimal Anticoagulation through Genetics Trial showed no improvement of a pharmacogenomics algorithm over a clinical algorithm at 4 weeks in a more diverse American population (24,25). Most recently, however, the multicenter, randomized Genetics Informatics Trial (GIFT) showed that genotype-guided warfarin dosing improved clinical outcomes versus clinically guided dosing. The rate of a composite of major bleeding, INR of four or greater, venous thromboembolism, or death was reduced from 14.7% to 10.8% in elderly patients undergoing elective hip or knee arthroplasty (26). Collectively, these trials show the importance of generalizability of results; measuring hard clinical outcomes versus surrogates, like INR; ethnic diversity in clinical trials; and the genotype coverage of pharmacogenomics testing. Future work will no doubt study cost-effectiveness and the effect of broader genotyping. In fact, in a recent prospective observational trial, de Oliveira Almeida *et al.* (27) found that other genetic variants (in *APOE*, *ABCB1*, and *UGT1A1*) were also associated with warfarin dose.

Current evidence-based CPIC guidelines for warfarin dosing include CYP2C9, VKORC1, and CYP4F2, and they are specific to patient self-identified ancestry. In non-African ancestry patients, the highest evidence is available for patients who carry at least one reduced function *CYP2C9* allele (*e.g.*, *2, *3), which predicts decreased hepatic clearance and lower dose requirements. Patients carrying a *VKORC1*–1639G>A allele are expected to have higher sensitivity to warfarin, thus requiring a lower dose. Individuals who have both of these variations require much lower doses of warfarin. Carriers of *CYP4F2* *3 allele may also require a 5%–10% increase in dose. In patients with African ancestry, because nearly one half of individuals may carry *CYP2C9* *5, 6, *8, *11, or rs12777823 variants, genotype-guided warfarin dosing is only recommended if testing covers these variants (23).

The FDA-approved product labeling contains recommendations for initial dosing with a convenient table on the basis of CYP2C9 and VKORC1 (28). Finally, Gage *et al.* (29), who led the GIFT, also maintain a web-based application (www.warfarindosing.org), which incorporates additional clinical and genetic data to provide tailored warfarin dosing in an easy-to-use interface. Neither tool currently incorporates kidney function in these recommendations.

Clopidogrel. Antiplatelet medications (prasugrel, ticagrelor, and clopidogrel) are indicated for patients who receive coronary artery stenting (30). They may also be used after kidney artery stenting, although the evidence for this is less robust (31). These drugs carry differing risks for bleeding, treatment failure, and cost, and their use is challenged by the lack of a well validated biomarker of treatment response. The most commonly prescribed drug, clopidogrel, is a prodrug that requires metabolic activation by CYP2C19 among other enzymes. Patients with decreased metabolic activity at CYP2C19 have decreased generation of the active metabolite and decreased platelet inhibition (32,33). Conversely, patients with increased CYP2C19 activity (rapid and ultrarapid metabolizers) may have increased generation of the active metabolite for clopidogrel and thus, a theoretically higher platelet inhibition and increased risk for bleeding. The National Institutes of Health–funded Implementing Genomics in Practice network's multicenter observational trial investigated patient outcomes with pharmacogenomics-guided antiplatelet therapy after percutaneous coronary intervention and stenting. Patients carrying at least one nonfunctional allele at *CYP2C19* who were treated with clopidogrel versus alternative therapy were at higher risk for major adverse cardiovascular events (hazard ratio, 2.26; 95% CI: 1.18 to 4.32; $P=0.01$) (34). This suggests that pharmacogenomics testing for CYP2C19 may provide a significant clinical benefit in real world clinical use. The CPIC guideline for clopidogrel therapy recommends that patients with at least one decreased function allele (*2, *3, *etc.*) receive an alternative agent due to risk for decreased response. Additionally, the guideline recommends that patients with increased metabolism (*1/*17 and *17/*17) be monitored for increased bleeding risk, although it does not recommend different dosing (35). Implementation of routine CYP2C19 testing in cardiac catheterization laboratories is feasible and has been a popular first pharmacogenomics implementation at several health systems (9).

Hyperlipidemia

Hepatic hydroxymethyl glutaryl–CoA reductase inhibitors (*e.g.*, simvastatin, atorvastatin, and "statins") are commonly used as cholesterol-lowering agents, but they are known for rare but significant myotoxicity that can progress to rhabdomyolysis. Although the risk for toxicity is low for most statin medications, high-dose (80 mg) simvastatin may carry a slightly higher risk than other statins (36). Additionally, this risk has been associated with a pharmacogenomics marker, which could allow clinicians to either prescribe a lower dose or use an alternative agent when it is detected (36). The polymorphic transporter gene *SLCO1B1* is responsible for uptake of simvastatin from the blood to hepatocytes, where it is metabolized. SLCO1B1 function is critical for simvastatin transport from blood to the liver, and when function is diminished, simvastatin blood concentrations are higher (increased systemic exposure) (36). Patients who carry at least one reduced function allele in *SLCO1B1* (*5, *15, or *17) should receive an alternative agent or a reduced dose of simvastatin. Providers should also consider routine creatinine kinase monitoring in this situation (37). Although other statins carry a risk for myotoxicity, SLCO1B1 plays little to no role in prediction because of drug lipophilicity and the predominant route of elimination (kidney elimination versus being a substrate for hepatic SLCO1B1) (37).

Transplantation

Kidney transplant is the treatment of choice for stage 5 CKD, and it is another area where pharmacogenomics can augment current precision medicine practices (38). Post-transplant medications have a narrow therapeutic index with interpatient variability that can be partially explained by genetic determinants. Evidence-based guidelines exist for several medications found in the post-transplant regimen, including azathioprine, tacrolimus, and voriconazole (13,39,40).

Azathioprine

Azathioprine is an antimetabolite used post-transplantation for long-term maintenance immunosuppressive therapy, and it is highlighted as a strategy to decrease costs for patients with kidney transplant (38). Azathioprine is a prodrug converted to mercaptopurine that undergoes methylation to inactive metabolites through polymorphic thiopurine methyltransferase (TPMT) (39). TPMT activity is influenced by genotype, and dosing recommendations are available to mitigate potential toxicities resulting from predictable pharmacokinetic changes (41,42).

Dose adjustments for initial dosing in patients with less or nonfunctional TPMT enzyme activity aim to reduce the risk of severe myelosuppression. Evidence-based guidelines recommend that patients who are *TPMT* heterozygous (one of the following alleles: *2, *3A, *3B, *3C, and *4) receive lower initial dosing of any thiopurine medication (azathioprine, mercaptopurine, or thioguanine). Patients with the homozygous variant genotype (two of the following alleles: *2, *3A, *3B, *3C, and *4) are at a substantial risk for severe, potentially life-threatening myelosuppression due to the accumulation of active metabolites (43). For patients with two nonfunctional *TPMT* alleles, guidelines recommend alternative therapy or an extreme dose decrease of azathioprine (39).

Tacrolimus

Tacrolimus is a calcineurin inhibitor that remains at the cornerstone of long-term immunosuppressant therapy post-transplantation. Clinical use is characterized by routine therapeutic drug monitoring due to its narrow therapeutic window and wide interpatient variability (38). Tacrolimus undergoes oxidative metabolism to inactive metabolites by CYP3A4/3A5 enzymes and can be affected by genetic variations in *CYP3A5* (44). Most whites (80%–85%) do not express CYP3A5 and may fall within standard, label-recommended dosing, whereas patients who express CYP3A5, prevalent in the black population as exemplified in the previous patient, may require higher doses (11,45).

A modified initial tacrolimus dosing on the basis of CYP3A5 metabolizer status is suggested if the genotype is known. In patients who express one or two functional copies of CYP3A5 (*e.g.*, *1 combinations; normal or intermediate metabolizers), guidelines recommend a starting dose 1.5–2.0 times higher than the typical starting dose, not to exceed 0.3 mg/kg per day. The goal for consideration of CYP3A5 metabolizer status in addition to other clinical factors is to reach therapeutic concentrations more quickly (13).

Voriconazole

Voriconazole is a triazole antifungal agent that is indicated in patients with kidney transplants and invasive fungal infection (46). Similar to aforementioned transplant agents, voriconazole has wide interpatient variability and a narrow therapeutic index, necessitating therapeutic drug monitoring (47). Metabolism of voriconazole occurs predominantly through CYP2C19 (40).

Evidence-based guidelines recommend alternative therapy or altered dosing for certain genotypes in efforts to avoid treatment failure and reduce the risk of adverse effects. In patients with CYP2C19 ultrarapid or rapid metabolizer status (*17/*17 or *1/*17, respectively), guidelines recommend an alternative agent due to unlikely achievement of target concentrations. Patients with CYP2C19 poor metabolizer status (two alleles of either *2 or *3) have a higher risk of adverse effects due to diminished metabolism, and an alternative agent not dependent on the CYP2C19 pathway is recommended (39).

Hyperuricemia

Elevated uric acid (hyperuricemia) is a frequent comorbidity in patients with CKD, and it is a contributor to the disease progression (48,49). Allopurinol is commonly prescribed to lower uric acid levels, and it is believed to be one of the leading causes of drug-related severe cutaneous adverse reactions (SCARs), including toxic epidermal necrolysis and Steven Johnson Syndrome (50). Risk for medication-induced SCAR has been associated with certain variants of the *HLA-B* gene from the MHC locus (51). Patients who carry at least one HLA-B*58:01 allele are at higher risk for SCAR from allopurinol (52). This allele was first discovered in East Asian populations and has since been detected and associated with SCAR from allopurinol in European populations (52,53). The CPIC guideline for allopurinol recommends against the use of allopurinol in patients who carry at least one HLA-B*58:01 allele (53,54),

but it does not provide a recommendation on whether to test patients preemptively (48,49).

Growing Evidence for Diabetes Treatments

Diabetic nephropathy is a leading cause for CKD and ESKD (55). As such, nephrologists treat many patients with comorbid type 2 diabetes mellitus who are managed on metformin. Although there are no clinical guidelines for the use of pharmacogenomics to tailor therapy with metformin, evidence has been growing that supports the use of the SNP rs11212617 in an intergenic (nongene) region of the genome called the chromosome 11 open reading frame 65 region. At this SNP, the presence of at least one "A" allele is associated with decreased response to metformin (56). In the future, this variation or others affecting pharmacokinetics (*e.g.*, transporters) may be useful for predicting which patients will require altered doses of metformin for adequate hemoglobin A1c control.

Clinical Decision Making and the Use of Pharmacogenomics in Practice

Several barriers prevent more widespread pharmacogenomics clinical implementation in everyday practice

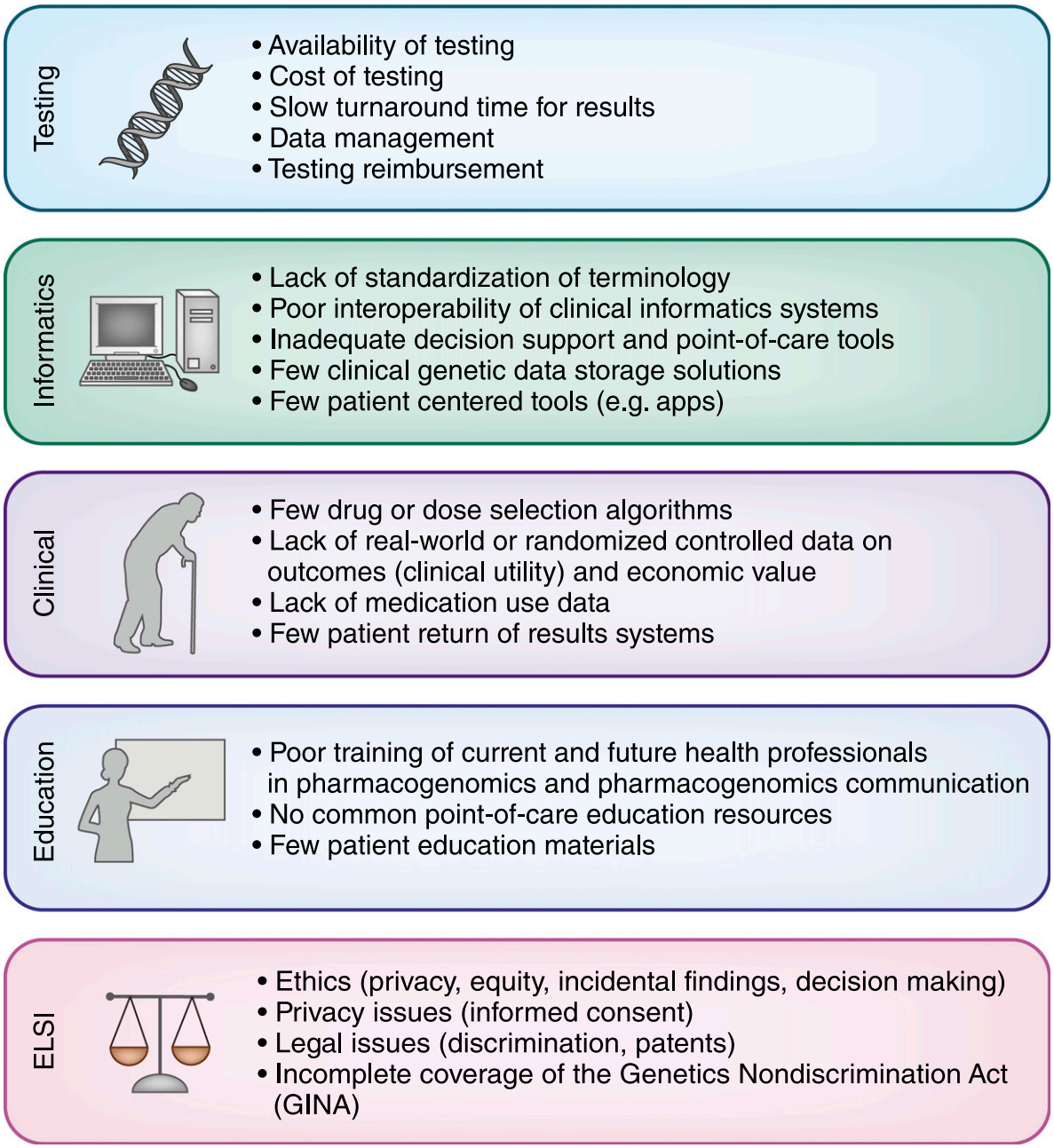

Figure 4. | **Pharmacogenomics implementation is limited by challenges in testing, informatics, clinical constraints, lack of education, and ELSI.** ELSI, ethical, legal, and social implications.

(Figure 4). Providers need to understand pharmacogenomics concepts for successful precision medicine clinical decision making, specifically whether they can apply the pharmacogenomics data within their current practice model, how the data should be integrated with other clinical parameters, and if a referral to a specialist should be made (*e.g.*, pharmacist, medical geneticist, or genetic counselor) (57). The addition of these data also creates a growing need for provider education. Strategies to train practicing providers and health care students to use pharmacogenomics in practice have been reviewed elsewhere (58) and range from clinical decision support at the point of care to education courses that allow learners to undergo personal genomic testing as a means of learning with one's own data (59).

Providers frequently face challenges with availability of testing and the origin of data, which may be from a new provider-initiated order, existing data from a previous pharmacogenomics result report, or patient-provided results from direct to consumer testing (*e.g.*, 23andMe, Mountainview, CA). It is necessary to ensure that testing was performed using an FDA-approved test or that it was done in a Clinical Laboratory Improvement Amendments environment with appropriate clinical validation (60). Germline (*i.e.*, genome from birth) genetic testing results generally do not change; thus, it may be cost saving to reuse test results. The testing technology used and testing coverage may vary (61). Although genome sequencing costs are plummeting, most clinical pharmacogenomics testing is accomplished using genotyping arrays targeting specific variants. It is prudent to evaluate what genes and variants were covered by the testing platform. For example, some commercial tests for CYP2C19 only test for *2 and *3, although at least eight additional low-prevalence star alleles are associated with decreased function and *17 is associated with increased activity (62).

The decision to order testing relies on the expected clinical utility of the data, availability and turnaround time of testing, and timeline for pharmacotherapy initiation. This can also be influenced by the potential broad application of data returned from a test, which may support future prescribing decisions (63). Deciding whether to test should also incorporate patient ancestry, specifically in patients in whom race/ethnicity can inform the probability of carrying one or more pharmacogenomic markers. For example, J.H. in the patient case was of African ancestry, which suggests higher probability that he carried at least one CYP3A5*1 allele (11). This is also evident for HLA-B*15:02, which predicts SCAR associated with carbamazepine and is found more often in those with Han Chinese ancestry (64). Regarding timing, warfarin therapy usually should not be delayed pending genetic data, but rather, the standard clinical algorithms should be initiated. If existing data are available or a genetic test with a rapid turnaround (<24 hours) is available, data may be actionable early enough to guide prescribing. However, for medications where genetic data can predict significant toxicity (*e.g.*, HLA-B), it may be prudent to wait for test results (65). Table 3 provides a practical summary of the decision-making process for whether to use pharmacogenomics.

Determining value of getting data before prescribing versus starting the medication immediately is tantamount to the argument of reactive versus preemptive pharmacogenomics testing. Reactive testing is the practice of ordering a pharmacogenomics test only when needed, which ensures that the testing is indicated (and increases the likelihood of payer reimbursement) at the expense of having to wait for results to be returned. Conversely, preemptive pharmacogenomics testing means that the worry of turnaround time is nonexistent, because the data are available before prescribing (66). Broad testing of many genes (*i.e.*, a pharmacogenomics panel) using a preemptive testing strategy is commonly advocated as the final step to make routine use of pharmacogenomics in practice cost effective (67). However, inadequate resources to support frontline providers for pharmacogenomics decision making and challenges in achieving payer reimbursement for preemptive testing limit these strategies (68).

Unique challenges and opportunities to integrating pharmacogenomics into the care of patients with kidney

Table 3. Clinical decision-making process for integrating pharmacogenomics in practice

Factor	Questions
Patient or population	Is the variant likely relevant in the patient or population? How common is the variant?
Quality of evidence	What is the strength of the evidence for the use of data? Are clinical guidelines or FDA recommendations available?
Testing	Is testing available? Is the coverage appropriate? What is the turnaround time of results?
Data availability	Does pharmacogenomics data already exist? Is the data quality sufficient to use?
Drug factors	How important is the gene/variant for the pharmacokinetics or pharmacodynamics of the drug? Does the drug have a narrow therapeutic index? Is the drug a prodrug or active? Will the variant decrease efficacy and/or increase toxicity?
Clinical factors	Are there other factors relevant to the decision, like timing of drug start or previous use of the medication? How do comorbid clinical conditions affect expected phenotypes? Are there drug-drug interactions that affect expected phenotypes?

FDA, Food and Drug Administration.

disease also exist. CKD is known to alter pharmacodynamic and pharmacokinetic relationships of several medications, particular those that rely on kidney elimination. In general, this scales with CKD stage and can be especially challenging in patients receiving dialysis (69). Nephrologists must also consider the systemic changes in patients with CKD, such as the changes in hepatic drug metabolism and other nonkidney clearance pathways that occur in patients with CKD (69). Phenocoversion is when there is a genotype-phenotype mismatch (*e.g.*, a normal metabolizer having a phenotype that looks like a poor metabolizer). The classic example is a drug interaction over-riding or masking the genotype-predicted phenotype. However, CKD could also be an extrinsic factor that may affect final drug response phenotypes. Future nephrology research should evaluate how to manage patients with CKD in this clinical scenario.

Despite the barriers to clinical pharmacogenomics, several large academic medical centers and increasingly, community providers are launching pharmacogenomics implementation programs (9,63). It is likely that the future will bring a greater expansion of precision medicine and enhanced data sharing between providers and patients. This will also add new opportunities to improve patient pharmacotherapy outcomes and additional risk that will need to be managed at all levels of clinical care and research (70,71).

Conclusions

Nephrologists care for patients with significant comorbidities and are challenged by wide interpatient variability in medication responses. They are ideally positioned to champion integration of pharmacogenomics to achieve precision medicine in the many disease areas affected by kidney disease. As pharmacogenomics knowledge expands, nephrologists will need to have familiarity with the state of the pharmacogenomics science, available pharmacogenomics resources and guidelines, contemporary application of pharmacogenomics data for specific drugs, and clinical decision-making approaches to using pharmacogenomics data.

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Disclosures

None.

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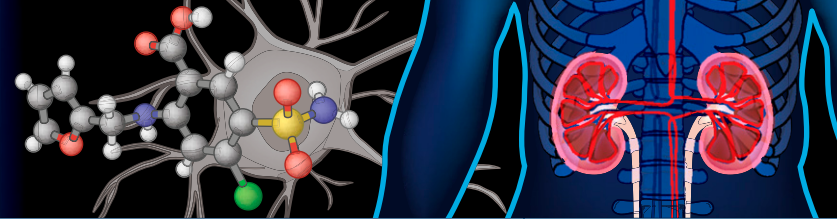

Medication Safety Principles and Practice in CKD

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Abstract

Ensuring patient safety is a priority of medical care because iatrogenic injury has been a primary concern. Medications are an important source of medical errors, and kidney disease is a thoroughfare of factors threatening safe administration of medicines. Principal among these is reduced kidney function because almost half of all medications used are eliminated *via* the kidney. Additionally, kidney patients often suffer from multimorbidity, including diabetes, hypertension, and heart failure, with a range of prescribers who often do not coordinate treatments. Patients with kidney disease are also susceptible to further kidney injury and metabolic derangements from medications, which can worsen the disease. In this review, we will present the key issues and threats to safe medication use in kidney disease, with a focus on predialysis CKD, as the scope of medication safety in ESKD and transplantation are unique and deserve their own consideration. We discuss drugs that need to be avoided or dose modified, and review the complications of a range of medications routinely administered in CKD, as these also call for cautious use.

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Introduction

Moliere, the 17th century playwright wrote, "Nearly all men die of their remedies, and not of their illnesses." Many therapeutic drugs used as remedies are kidney-relevant, meaning they require clearance or metabolism by the kidney or have potential for nephrotoxicity (1,2). One important barrier to medication safety is CKD is often under-recognized (3,4). Failure to recognize patients with CKD is a lost opportunity to minimize patient safety threats related to medications. A study alerting providers of medication orders requiring modifications because of impaired kidney function revealed 14% of all orders were for kidney-relevant medications (5). Of these, about 15% were flagged with an initial prescription error. Others have found a higher proportion of medication orders with potential nephrotoxicity, or orders not properly modified for kidney function, which are therefore associated with high risk of adverse events for both kidney-relevant and nonkidney-relevant medications in CKD (6,7).

Adverse medication-related outcomes in CKD can be classified as those leading to kidney damage, including AKI, accelerated kidney function loss, and ESKD, as well as other metabolic complications, including hyperkalemia, hypercalcemia, hypoglycemia, and bleeding, among others (8). Omitted therapies, such as failure to initiate erythropoiesis-stimulating agents (ESAs) for severe anemia, can also be considered safety events. A substantial proportion of the burden of illness in patients with CKD relates to such safety complications, and may be prevented with improved attention to this population's special care needs.

Safe medication use in CKD is a complex process involving determination of kidney function, consideration of changes in drug pharmacokinetics (PK) and pharmacodynamics (PD) as kidney function declines, and judicious use of therapies to manage uremic complications and other comorbid conditions (9).

The US Food and Drug Administration (FDA) guidance for dosing recommendations accounting for kidney function were not issued until 1998. Although initial FDA guidance called for direct measurement of GFR using a tracer such as iothalamate, the 2000s witnessed the validation and implementation of estimating equations to assess kidney function (9). Yet, estimates of kidney function on the basis of creatinine clearance (*e.g.*, the Cockcroft–Gault equation) and GFR (*e.g.*, the CKD Epidemiology Collaboration equation) can differ substantially from direct measurement of kidney function. These discrepancies can lead to misguided dosing recommendations for certain drugs (10). However, direct measurement of kidney function is often not practical; hence, a Kidney Disease Improving Global Outcomes (KDIGO) consensus panel recommended that clinicians' refer to a valid equation for determination of eGFR (9). Dosing adjustments should be made on the basis of clinically observed drug response and toxicity, as well as drug levels, when measurable.

Altered drug PK/PD profiles in CKD may warrant modified dosing or drug discontinuation (8,9,11). Drug absorption in the gastrointestinal (GI) tract may be impaired by medications that alter gastric pH (*e.g.*, proton pump inhibitors) and comorbid conditions that cause edema (*e.g.*, congestive heart failure [CHF]) or GI losses common in CKD (*e.g.*, diarrhea) (11). The volume of distribution of water-soluble drugs may also be increased in the setting of edema. Uremia in CKD can also alter the volume of distribution of plasma/tissue protein-bound drugs,

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which can significantly affect therapeutic and safety outcomes of narrow therapeutic range medications (*e.g.*, digoxin) (11). Changes in hepatic or nonrenal clearance of commonly used medications, such as antibiotics and antihypertensives, have also been observed in CKD (12). All mechanisms of kidney excretion are impaired in CKD, including glomerular filtration, tubular secretion, and reabsorption (11). Progressive decline in kidney function results in changes in clearance, therapeutic effect, and risk of toxicity of many drugs eliminated through the kidneys.

Medication Safety in CKD and Related Complications

In addition to a medication's nephrotoxic effects, patients with CKD are also susceptible to other adverse effects with agents routinely used in the management of CKD and comorbid conditions. Examples include anticholinergic (*e.g.*, histamine-1 receptor antagonists), sedative (*e.g.*, codeine, diazepam), and hypoglycemic (*e.g.*, glyburide) effects, as well as electrolyte abnormalities (*e.g.*, renin-angiotensin-aldosterone system [RAAS] blockers, sulfamethoxazole-trimethoprim, mineralocorticoid receptor antagonists, calcium- and magnesium-containing antacids). Agents with particular pertinence to patients with CKD are discussed below.

Diuretics

Thiazide and loop diuretics are commonly used for natriuresis and BP control with a reduced GFR. This is especially important in advanced CKD, where extracellular volume excess is a concern and BP becomes more salt-sensitive. Loop diuretics are the preferred agents at GFR<30 ml/min per 1.73 m^2, but more potent thiazide diuretics also can be used, often in combination with loop diuretics. Injudicious diuretic use can increase the risk of AKI in vulnerable patients with CHF, ascites, or other edematous states, especially with superimposed volume depletion (13). Loop and thiazide diuretics are also associated with a range of electrolyte disturbances, including hypokalemia, hypomagnesemia, and hypochloremic metabolic alkalosis (14,15). Additional metabolic derangements include hyperuricemia, and at higher doses of thiazide diuretics, glucose intolerance and hyperlipidemia (13).

RAAS Blockers as a Double-Edged Sword

RAAS blockers are essential to CKD treatment and although not overtly nephrotoxic, under certain clinical circumstances they have the potential for harm (16). Practitioners may construe physiologic reductions in GFR with RAAS blockers as justification to avoid these agents with advanced CKD; however, RAAS blockers have demonstrated benefit in early as well as later stages of CKD (17). Hazards from RAAS blockers are most prominent in conditions where the kidney is autoregulation-dependent, including CHF, active diuresis, and other illnesses with attendant volume depletion (16).

Hypotension with RAAS blockers is common among elderly patients, and episodes of AKI across the range of severity are not infrequent among nursing home patients treated with RAAS blockers (16,18). AKI is also more common with treatment with RAAS blockers during high summer temperatures and with volume depletion, and can also occur with bilateral renal artery stenosis or unilateral stenosis with a solitary kidney (19). Patients with CHF on angiotensin-converting enzyme inhibitors develop a greater rate of AKI with intensified diuretic regimens than their counterparts on lower doses or no diuretics (20). Adding a nonsteroidal anti-inflammatory drug (NSAID) to an RAAS blocker and diuretic can amplify the risk of AKI, and has been described as a "triple whammy." (21) Similar conditions may increase the risk of AKI when more than one RAAS blocker are used together, or in combination with sodium-glucose cotransporter 2 in patients with CKD and diabetes (22,23). An increase in AKI admissions have been reported and correspond with a rise in RAAS blocker prescriptions across geographic regions. AKI admissions increased as much as 15% because of an increase in RAAS blocker prescriptions (24).

Dyskalemia

Hyperkalemia and hypokalemia are common safety concerns for patients with CKD because they can lead to altered cardiac electro-conduction, arrhythmias, and sudden death (25–30). Hyperkalemia can occur with RAAS blocker use, especially when two are used in combination, or with other drugs including potassium-sparing diuretics, NSAIDs, or trimethoprim-sulfamethoxazole (31). Less commonly, heparin can cause hyperkalemia in the setting of AKI, or when used with other agents that increase the risk of hyperkalemia (32). It is also important to note that hypokalemia can develop with unsupervised diuretic use (33).

Several tactics in response to hyperkalemia can shift potassium from the extracellular to intracellular space (*e.g.*, insulin and glucose, β-agonist therapy, and bicarbonate in the setting of acidosis), but definitive therapies remove total body potassium. These treatments includes diuresis, which may have limited effectiveness and the potential for metabolic or hemodynamic complications. Cation exchange resins, such as sodium polystyrene sulfate, have limited evidence for efficacy in potassium removal, and have associated concerns for toxic effects including bowel necrosis (34). However, this complication is uncommon, with unclear linkage to oral versus rectal administration (35). The cation exchange resin patiromer has introduced an alternative for chronic treatment of hyperkalemia, and can be used in conjunction with RAAS blockers (36). However, patiromer has been associated with hypomagnesemia and altered absorption of some common drugs (37). Mineralocorticoid agonists may have modest effectiveness in reducing serum potassium, especially in hyperkalemic patients on dialysis (38). Dialysis remains the gold standard for potassium removal, but should be used sparingly, except for patients with ESKD (25). Treatment and prevention of hypokalemia includes reduction in diuretic use, sodium restriction, and liberalization of patients' diets to include potassium-rich foods. Consideration of potassium-sparing diuretics and RAAS blockers, where appropriate, should also be considered (33).

Treatments for Anemia in CKD

Anemia management in CKD is a balance between optimizing erythropoiesis and minimizing adverse effects associated with therapeutic agents that treat anemia (39,40). Use of ESAs along with iron supplementation to

treat anemia are important elements in CKD care (40). Despite extensive experience with these agents, many questions remain regarding optimal and safe therapeutic end points (39–41).

Iron supplementation (oral or intravenous) is usually the first step in anemia management (40,42). However, oral iron use is often limited because of suboptimal efficacy and GI intolerance (43,44). Intravenous iron is more efficacious at correcting iron deficiency, improving hemoglobin levels, and reducing ESA use and blood transfusions, but is often underutilized because of clinician apprehension of infusion-related reactions and iron overload (42,43). Anaphylaxis most commonly occurs with high molecular weight iron dextran, whereas severe or life-threatening reactions are rare with nondextran formulations, such as iron sucrose and sodium ferric gluconate complex (42,45). Commentaries have postulated that aggressive iron supplementation and overload in conjunction with ESA use may increase the risk of safety events (46). The upper limits of iron stores is clinically undefined, but studies suggest that adverse effects related to iron overload are not likely to occur at ferritin levels below 1200–2000 ng/ml (42,45). However, the KDIGO guidelines take a conservative stance with regard to upper limits of iron stores, and do not recommend routine use of iron supplementation when transferrin saturation and ferritin levels are adequate (40).

Controversy continues over appropriate ESA use, and there are safety concerns about optimal treatment targets in CKD (47–50). Generally, trials evaluating aggressive treatment targets with epoetin alfa have been successful at achieving hemoglobin targets, but demonstrate a higher rate of arteriovenous fistula thrombosis, myocardial infarction, death, and CHF-related hospitalizations. Comparable results have been reported with darbepoetin alfa (48). Apart from a modest improvement in quality of life with higher hemoglobin targets, aggressive treatment has been associated with an increased risk of stroke, venous thromboembolism, and death in patients with an active malignancy (40). Hence, the benefits of targeting higher hemoglobin levels with ESAs are limited by significant toxicity signals (50,51). As part of best practices identified by the American Society of Nephrology's "Choosing Wisely" campaign, an individualized patient approach to ESA use is recommended to alleviate symptoms while maintaining conservative hemoglobin targets and minimizing the need for transfusions (52). Specifically, ESAs should be avoided in asymptomatic patients who are predialysis, with hemoglobin levels >10 g/dl. When treatment is warranted, ESAs should be used judiciously, along with close monitoring of hemoglobin and anemia symptoms.

Treatments for CKD–Mineral and Bone Disorder

CKD–mineral and bone disorder (CKD–MBD) is a complex condition characterized by phosphate, calcium, vitamin D, and parathyroid hormone (PTH) abnormalities (53). Pharmacotherapeutic interventions have primarily focused on correcting laboratory disturbances with the intent of reducing long-term complications. Paradoxically, drug therapy for CKD–MBD has the potential to accelerate disease progression if not used appropriately.

Maintaining phosphorus and calcium homeostasis in CKD is associated with decreased kidney and cardiovascular risk (54). Phosphate binders are the recommended first-line therapy in CKD to correct hyperphosphatemia (55). However, binders do not significantly improve phosphorus levels or delay the progression of coronary artery calcification in the predialysis CKD population (56–59). The updated 2017 KDIGO guidelines de-emphasize targeting precise calcium and phosphate levels, but endorse the initiation and adjustment of therapy on the basis of "persistent and progressively" abnormal individual levels in the context of overall trends in CKD–MBD biomarkers (55,57).

Noncalcium-based binders may have less effect on calcium balance and cardiovascular endpoints (60). Specifically, novel iron-based phosphate binders are effective alternatives to managing hyperphosphatemia and minimizing risk of hypercalcemia, and have an added benefit of improving iron stores (61). When cost limits choice to calcium-based binders, the dosing should be tailored to the individual patient's dietary calcium intake to maintain a neutral calcium balance (59). Calcium-containing binders should be considered primarily in patients with CKD with low calcium intake. Calcium-based products should be avoided in patients with adequate (800–1000 mg/d) or excessive intake. Examples of surreptitious calcium intake include over-the-counter antacids, and patiromer used in the treatment of hyperkalemia.

Calcitriol and other vitamin D receptor antagonists (VDRA) suppress parathyroid gland activity in advanced stages of CKD (55). However, there may be a negative shift in the risk–benefit profile for VDRAs in predialysis CKD because their use is associated with increased risk of hypercalcemia with no significant benefit to cardiac function (62). The current guidelines recommend avoiding routine use of VDRAs before ESKD (55). When therapy is warranted, VDRAs should be used conservatively and only with evidence that intact PTH levels are progressively and/or persistently elevated.

Calcimimetics are also efficacious at suppressing PTH secretion in CKD–MBD (55,63). This class of agents is commonly associated with hypocalcemia in patients with ESKD and patients who are predialysis, however, the clinical significance of this expected safety event is unclear (55). Calcimimetics are not recommended in CKD GFR categories 3a-5 (G3a–G5) when the patient is not on dialysis, but are limited to use in CKD category G5 when the patient is on dialysis (55). Additionally, the guidelines recommend an individualized approach to managing hypocalcemia on the basis of severity of symptoms and calcium levels.

Antihyperglycemic Agents in CKD

Poorly controlled type 2 diabetes (T2DM) mellitus can lead to microvascular complications, including nephropathy, as >40% of patients with T2DM have CKD (64). Slowing the progression of nephropathy through glycemic control is of paramount importance in clinical management.

Metformin remains the first-line treatment for T2DM, given its hemoglobin A1c lowering potential, oral administration, neutral effect on body weight, and cardiovascular outcome and all-cause mortality benefit (65). Historically, metformin was contraindicated in patients with a serum creatinine level of ≥1.5 or ≥1.4 mg/dl for men and women, respectively, given that the drug is eliminated through the kidneys and can increase the risk of lactic acidosis (66). However, this is an exceedingly rare complication and most

Table 1. Cautionary notes for prescribing in people with CKD

Medication	Comments
Narrow therapeutic index drugs	
Aminoglycosides	Nephrotoxic (acute tubular necrosis, AKI). Ototoxic. Therapeutic drug monitoring recommended.
Digoxin	Increased for digoxin toxicity including arrhythmias. Therapeutic drug monitoring recommended.
Lithium	Diabetes insipidus, interstitial disease. Avoid concomitant use of thiazide diuretics and NSAIDs, maintain hydration. Therapeutic drug monitoring recommended.
Phenytoin	Low albumin will affect bound concentration. Monitor free phenytoin level.
Tacrolimus	Vasoconstriction, nephrotoxicity. Avoid concomitant use of CYP 3A4 inhibitors. Therapeutic drug monitoring recommended.
Warfarin	Increased risk of bleeding. Close INR monitoring recommended.
Analgesics	
NSAIDs	Hemodynamically mediated kidney injury, sodium and/or potassium retention, interstitial nephropathy. Avoid with concomitant use of diuretics or RAAS inhibitors, maintain hydration, consider alternate analgesic.
Meperidine	Active metabolite, normeperidine, increases risk of seizure. Avoid.
Morphine	Active metabolites, increased drug effect.
Contrast agents	
Iodinated contrast media	Nephrotoxic. Use lowest dose, maintain hydration with saline, can consider N-acetylcysteine or sodium bicarbonate, avoid concomitant nephrotoxins, avoid use of high-osmolarity agents, avoid use of gadolinium-containing contrast media.
Bowel preparation	
Phosphate-containing bowel preparation	Increased risk for phosphate nephropathy and electrolyte disturbances. Avoid phosphate-based preparations.
Herbals	
Licorice	Increased risk of sodium and water retention, hypokalemia, hypertension. Avoid use.
Noni juice	Increased risk of hyperkalemia. Avoid use.
St. John's wort	CYP inducer. Increased risk of drug interactions. Avoid use.
Ginkgo biloba	Increased risk of bleeding. Avoid use.
Ephedra alkaloids (ma huang)	May potentiate hypertension. Avoid use.

Excerpted from the 2012 Kidney Disease Improving Global Outcomes Guidelines on the management of CKD (77). NSAIDs, nonsteroidal anti-inflammatory drugs; CYP 3A4, cytochrome p450 3A4; INR, International Normalized Ratio; RAAS, renin-angiotensin-aldosterone system; CYP, cytochrome p450.

patients with mild-to-moderate kidney impairment safely tolerate metformin (66). Nonetheless, although the incidence remains low, the risk of lactic acidosis or elevated lactate concentrations increases with metformin use with declining kidney function, especially when higher doses are used. In 2016, the FDA required changes to metformin labeling to expand its use in patients with impaired kidney function (Table 1) (67). The guidelines also recommend using GFR to estimate kidney function rather than serum creatinine to determine whether a patient is a safe candidate for metformin.

The American Diabetes Association advocates considering both efficacy and safety profiles when selecting an agent to add to metformin (65). Patients with T2DM and CKD are at an increased risk for hypoglycemia, and some agents pose a higher risk of hypoglycemia than others. Sulfonylureas and insulin have a higher risk for hypoglycemia than other drug classes. Within the sulfonylurea class, glyburide is not recommended for use in CKD because it is hepatically metabolized with active metabolites excreted by the kidney (68). Glimepiride is metabolized in the liver into two major metabolites, and clinical trials have demonstrated a reduced elimination of these metabolites with kidney impairment; therefore, to reduce the risk of hypoglycemia, the drug should be initiated at a low dose in patients with T2DM and CKD. Glipizide is also metabolized by the liver but into inactive metabolites excreted by the kidney; hence, it is the preferred sulfonylurea agent for use in CKD.

Thiazolidinediones are highly metabolized by the liver and require no dose adjustments in CKD (68). Despite this, the thiazolidinedione class of agents is often avoided because of a propensity for fluid retention and edema in CKD.

Two classes of incretins available for the treatment of T2DM have grown in use over the last decade: dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists. All dipeptidyl peptidase-4 inhibitors agents can be safely used in all stages of CKD, and ESKD on dialysis (69). Certain agents in this class are eliminated through the kidneys, such as alogliptin, saxagliptin, and sitagliptin, and require a dose adjustment with lower GFRs. Linagliptin is eliminated through a hepatobiliary route and does not require adjustment, offering an advantage over the other members in the class (70).

Each of the six available glucagon-like peptide-1 receptor agonists differ in their recommendations for use in CKD,

Table 2. Dosing recommendations for select drug therapies by CKD stage

Drug Class	Drug	CKD Staging by GFR Category (ml/min per 1.73 m^2)					
		Stage 1 (>90)	Stage 2 (89–60)	Stage 3a (59–45)	Stage 3b (44–30)	Stage 4 (29–15)	Stage 5 (<15)
Biguanide	Metformin	R	R	R	DA[a]	X	X
Sulfonylureas	Glipizide	R	R	R	R	R	R
	Glimepiride	R	R	R	R	R	C
	Glyburide	R	R	C	C	C	C
Thiazolidinediones	Pioglitazone	R	R	R	R	R	R
	Rosiglitazone	R	R	R	R	R	R
DPP4 inhibitors	Alogliptin	R	R	DA	DA	DA	DA
	Linagliptin	R	R	R	R	R	R
	Saxagliptin	R	R	R	DA	DA	DA
	Sitagliptin	R	R	R	DA	DA	DA
SGLT2 inhibitors	Canagliflozin	R	R	DA	X	X	X
	Dapagliflozin	R	R	X	X	X	X
	Empagliflozin	R	R	R	X	X	X
	Ertugliflozin	R	R	X	X	X	X
Direct oral anticoagulants for indications: VTE/ atrial fibrillation	Apixaban	R/DA[b]	R/DA[b]	R/DA[b]	R/DA[b]	R/DA[b]	C/DA[b]
	Dabigatran	R/R	R/R	R[c]/R[c]	R[c]/R[c]	C/DA[d]	C/C
	Edoxaban	R/X[e]	R/R	DA[f]/DA[f]	DA/DA	DA/DA	X/X
	Rivaroxaban	R/R	R/R	R/DA[f]	R/DA	X/DA	X/C
ARB/neprilysin inhibitor	Sacubitril/Valsartan	R	R	R	R	DA[g]	DA[g]
Antiretrovirals	TDF	R	R	DA[f]	DA	DA	DA
	Emtricitabine	R	R	DA[f]	DA	DA	DA
	Lamivudine	R	R	DA[f]	DA	DA	DA
	Elvitegravir/Cobicistat/ Emtricitabine/TDF	R	R[h]	X[f]	X	X	X
	TDF/Emtricitabine[i] Abacavir/Lamivudine Efavirenz/Emtricitabine/ TDF Rilpivirine/Emtricitabine/TDF Dolutegravir/Abacavir/Lamivudine	R	R	X[j]	X[j]	X[j]	X[j]
	Tenofovir Alafenamide/ Emtricitabine Elvitegravir/Cobicistat/ Tenofovir Alafenamide/Emtricitabine Emtricitabine/Rilpivirine/ Tenofovir Alafenamide	R	R	R	R	X	X
Direct-acting antihepacivirals	Ledipasvir/Sofosbuvir Sofosbuvir/Velpatasvir Sofosbuvir/Velpatasvir/Voxilaprevir Simeprevir Sofosbuvir	R	R	R	R	C[k]	C[k]
	Ombitasvir/Paritaprevir/Ritonavir Elbasvir/Grazoprevir Glecaprevir/Pibrentasvir Daclatasvir	R	R	R	R	R	R

R, can be safely recommended at normal doses; DA, dose adjustment required for use; X, use not recommended; C, no manufacturer specific recommendation for use or dose adjustment, use with caution; DPP4, dipeptidyl peptidase-4; SGLT2, sodium-glucose co-transporter 2; ARB, angiotensin receptor blocker; VTE, venous thromboembolism; TDF, tenofovir disoproxil fumarate; CrCl, creatinine clearance; P-gp, P-glycoprotein.

[a]Metformin should not be initiated in patients with an eGFR between 30 and 45 ml/min per 1.73 m^2.

[b]Apixaban requires dose adjustment in atrial fibrillation if two of the following characteristics are met: serum creatinine ≥1.5 mg/dl, body weight ≤60 kg, age ≥80 years.

[c]Dabigatran requires dose adjustment in both VTE and atrial fibrillation for CrCl 30–50 ml/min with coadministration of P-gp inhibitors.

[d]Avoid dabigatran use in atrial fibrillation for CrCl <30 ml/min with coadministration of P-gp inhibitors.

[e]Avoid edoxaban use in atrial fibrillation for CrCl >95 ml/min because of increased risk of ischemic stroke.

[f]Requires no dose adjustment for CrCl 51–59 ml/min (edoxaban in VTE and atrial fibrillation, rivaroxaban in atrial fibrillation, ceftazidime/avibactam, ceftolozane/tazobactam, tenofovir disoproxil fumarate) or CrCl 50–59 ml/min (emtricitabine, lamivudine, elvitegravir/cobicistat/tenofovir disoproxil/emtricitabine) or eGFR 50–59 ml/min per 1.73 m^2 (meropenem/vaborbactam).

[g]Dose adjustment required for initial dose.

[h]Avoid initiating Elvitegravir/Cobicistat/Emtricitabine/TDF in CrCl <70 ml/min.

[i]Dose adjustment may be used for TDF/Emtricitabine in CrCl 30–49 ml/min.

[j]Use individual components. Dose adjustment for TDF and Emtricitabine for kidney function.

[k]No dose adjustments have been provided by the manufacturer in CrCl <30 ml/min.

Table 3. Approach to medication assessment and deprescribing in CKD (8,9,11,77,79)

Step	Comments
1. Assess kidney function	Determine GFR to evaluate kidney function for drug dosing Direct measurement of GFR may be necessary for dosing narrow therapeutic or toxic range drugs
2. Medication history	Collect complete medication list: Include all prescription, over-the-counter and dietary supplements (including herbal, nonherbal, and vitamin supplements) Collect history of drug allergies/sensitivities; adjustment or discontinuation of medication due to impaired kidney function or toxicity
3. Medication review	Is the drug nephrotoxic or contraindicated in CKD or at a specific GFR level? Is the drug or drug metabolite's half-life prolonged in CKD? Is the risk of adverse effects or drug–drug interactions increased in CKD? Does this drug have a narrow therapeutic or toxic range?
4. Adjust regimen	Prescribing: Calculate/adjust dose on the basis of Food and Drug Administration-approved product labeling, drug pharmacokinetic characteristics, and the patient's GFR Refer to peer-reviewed literature recommendations if limited information in product labeling Patients should consult with pharmacist or health professional before initiating over-the-counter medications or dietary supplements Deprescribing: Discuss rationale and plan with patient and care team Deprescribe one medication at a time, consider agents with greatest harm and least benefit, consider patient preferences
5. Drug therapy monitoring	Document and monitor for signs efficacy, toxicity, and change in symptoms with initiation or discontinuation of agent Revise regimen on the basis of acute (*e.g.*, intercurrent illness) or chronic changes/decline in patient's health status and/or kidney function

partly because of the paucity of data evaluating use with impaired kidney function. Exenatide and exenatide extended release should be avoided in patients with a creatinine clearance <30 ml/min because both are eliminated through the kidneys, whereas lixisenatide should not be used for patients with a creatinine clearance of <15 ml/min (70). Other agents, such as albiglutide, dulaglutide, and semaglutide, are not associated with kidney elimination and do not require a dose adjustment with impaired kidney function. Liraglutide is not eliminated through the kidneys but does carry a cautionary recommendation for use with any degree of kidney impairment (70,71). Liraglutide is also unique in this class because its use has been specifically evaluated in patients with CKD stage 3, revealing no negative effects on kidney function, and in patients with CKD stage 4, showing a slower progression of diabetic kidney disease (72,73). Finally, there have been postmarketing reports of both acute kidney failure and worsening of CKD in both patients with and without reduced kidney function for several agents in this class (70). The majority of these are in patients experiencing GI adverse effects, and the drug class carries a warning to monitor kidney function in patients with CKD who report severe GI symptoms.

The sodium-glucose cotransporter 2 inhibitors are oral agents for treatment of T2DM targeting kidney tubular glucose reabsorption. Efficacy of these agents can be affected by kidney function and specific dosing recommendations are summarized in Table 2 (74).

Finally, all available insulin preparations can be used in patients with CKD. However, because the kidney is responsible for 30%–80% of insulin removal, patients should be monitored for hypoglycemia due to decreased insulin elimination as kidney function declines (75). Insulin requirements should be tailored to meet individual needs, and no specific dose adjustment is recommended.

Anticoagulant Agents in CKD

Many patients with CKD require anticoagulation for comorbid conditions and treatment with vitamin K antagonist or direct oral anticoagulants (DOACs). However, caution is warranted with DOAC use in CKD because these agents are partly eliminated by the kidneys (76). Unaltered dosing can result in an increased risk of bleeding. Although all DOACs can be used with impaired kidney function, the recommendations for dose adjustment are dependent on indication and kidney function. Of note, DOACs should be avoided in ESKD given the lack of data evaluating the efficacy and safety of these agents (76). Low molecular weight heparin should also be administered at a reduced dose with lower GFRs, and avoided in ESKD.

Medication Reconciliation and Deprescribing in CKD

Several approaches have been proposed to address medication safety hazards in CKD (8,11,77) Much of the focus is on adherence to appropriate prescribing guidelines, medication reconciliation, evidence-based agent selection, dose modifications on the basis of altered kidney function and drug PK/PD, and monitoring of drug therapy response and kidney function (8,9,11). Special attention is also required for CKD drug dosing with many over-the-counter medications and dietary supplements (*i.e.*, herbal supplements, nonherbal supplements, and vitamins) (78). However, it is difficult to provide dosing and management recommendations for many herbals and vitamins with unknown toxicities.

The KDIGO guidelines provide a starting point for evaluating medication appropriateness for commonly used medications in CKD (Table 1). Since publication of the guidelines, a number of new agents used in management

of common comorbid conditions entered the market. Of these new agents, we have identified several drug classes and selected agents that may require dose adjustment or deprescription in CKD, detailed in Table 2. Decision-support platforms such as Micromedex and Lexicomp offer easily accessible monographs of prescription and over-the-counter medications to guide agent selection and dosing. The Natural Medicine Comprehensive Database is a useful resource to consider the safety of herbals, dietary supplements, vitamins, and other and nutraceuticals in CKD.

In addition to adherence to prescription guidelines, deprescribing is gaining attention for identifying and eliminating inappropriate medications. Deprescribing can be defined as "the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits." (79) Studies involving deprescribing or drug therapy reviews in kidney disease have centered on the hemodialysis population, and deprescribing guidance for patients with predialysis CKD are lacking (80,81). Despite the paucity of guidelines for this population, health care providers can apply general principles of deprescribing in CKD (8,11,79).

A range of drug classes are candidates for deprescription in CKD. NSAIDs are priority for deprescribing in CKD because of potential adverse effects such as worsening of CKD, fluid retention, hyperkalemia, BP, and AKI (52,77,82). NSAIDs, including cyclooxygenase-2 inhibitors should be avoided in hypertension, CHF, and CKD of all causes (52). Other candidate drug classes for deprescribing in CKD include proton pump inhibitors, for which growing evidence indicates potential kidney and nonkidney-related harm with prolonged usage (83).

A general approach to medication assessment and deprescribing is proposed in Table 3. As outlined in the table, one should review the indication for each individual agent to determine whether the potential for harm outweighs the evidence for efficacy. For example, RAAS blockers, which can lead to hyperkalemia and AKI, should undergo a harm versus benefit evaluation, especially in patients where the benefits of treatment targets are unknown or equivocal.

Finally, given the complexity of medication management of the CKD population, there is strong justification for the involvement of an interprofessional team that includes pharmacists to prevent, identify, and resolve potential or actual medication-related problems (84,85). Although much of the evidence supporting pharmacist involvement in medication reconciliation and management is in the hemodialysis population, these best practices may also be extrapolated to the predialysis population.

Summary

Medication management in CKD offers unique challenges, but presents providers with opportunities to enhance care quality to this high-risk population. Implementing strategies to evaluate the heavy medication burden of many patients with CKD, considering the risks and benefits of all prescribed agents, and deprescribing when indicated may improve patient outcomes. The implications of reduced kidney function in a disease population with a range of comorbidities are substantial, and recognizing these can have a significant effect on care management of patients with CKD, and has the potential to reduce much of their morbidity and mortality.

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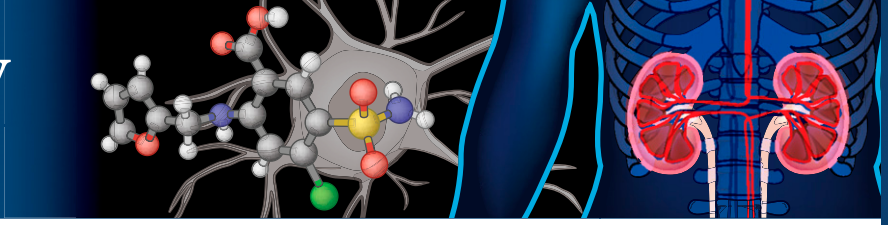

Pharmacology behind Common Drug Nephrotoxicities

Mark A. Perazella

Abstract

Patients are exposed to numerous prescribed and over-the-counter medications. Unfortunately, drugs remain a relatively common cause of acute and chronic kidney injury. A combination of factors including the innate nephrotoxicity of drugs, underlying patient characteristics that increase their risk for kidney injury, and the metabolism and pathway of excretion by the kidneys of the various agents administered enhance risk for drug-induced nephrotoxicity. This paper will review these clinically relevant aspects of drug-induced nephrotoxicity for the clinical nephrologist.

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Introduction

Medications are a relatively common cause of kidney injury (1–12). The epidemiology of drug-induced nephrotoxicity is currently based on literature focusing on AKI. Drug-induced nephrotoxicity in adults is approximately 14%–26% in prospective cohort studies of AKI, whereas 16% of hospitalized AKI is due to drugs in the pediatric population (1–4). Drug-induced nephrotoxicity is more common in hospitalized patients, in particular intensive care unit patients (2,5).

Importantly, the general population is exposed to a large number of prescribed and over-the-counter drugs as well as a variety of substances available at health food stores (natural products, supplements, herbal remedies) (6–20). Various imaging agents used for diagnostic purposes are also associated with nephrotoxicity (21–23). However, not all patients exposed to the various potential nephrotoxins develop kidney disease. Thus, the nephrotoxicity of medications, drugs, and other ingested substances is a complicated process that involves a combination of factors. These include the inherent nephrotoxic potential of the drug, underlying patient characteristics that enhance their risk for kidney injury, and the metabolism and excretion of the potential offending agent by the kidney (6–9).

As part of the *Clinical Journal of the American Society of Nephrology* series "Nephropharmacology for the Clinician," this review will cover some of the common nephrotoxic drugs that the kidney is exposed to in clinical practice, the factors that increase vulnerability of the kidney to these potential toxins, provide insight into the mechanisms by which kidney injury occurs, and cover some of the associated clinical kidney syndromes that develop in response to these agents (1–33).

Factors Associated with Drug-Induced Nephrotoxicity

The development of drug-induced nephrotoxicity can be best understood by examining the factors that contribute to nephrotoxicity (1–9). Exposure to a potentially nephrotoxic medication is an obvious requirement. Drugs may be modestly nephrotoxic or maintain high risk to cause kidney injury on the basis of their structure, dose, metabolic handling, excretory pathway through the kidney, and other characteristics (5–9). Underlying patient characteristics, such as comorbid conditions, genetic determinants of drug metabolism and transport, and immune response genes, are also important in drug nephrotoxicity (5–9). As the kidney metabolizes and excretes (through filtration and tubular secretion) many ingested drugs, the interaction of these substances with various parts of the nephron may be associated with nephrotoxicity (5–9). For kidney injury to occur, some combination of these three risk factors is generally present. More often than not, more than one is present. It is the differences in structure of the ingested drug, underlying patient characteristics, and alterations in kidney handling of the ingested substance that likely explain the variability and heterogeneity observed with drug-induced nephrotoxicity.

The Drug

The initial step in the development of kidney injury involves exposure to a potentially toxic offending agent. The general population is exposed to a variety of potential nephrotoxic substances including prescribed therapeutic agents, over-the-counter products, diagnostic agents, and environmental substances (Table 1). Examples of potentially nephrotoxic drugs that are utilized to treat various disease processes include antimicrobial agents, anticancer drugs, analgesics, and immunosuppressive agents (1–34). Furthermore, a large number of new medications with unknown nephrotoxic potential make it through clinical trials and are subsequently released into clinical practice where they cause kidney injury. This is likely related to exposure of these new drugs in patients who have comorbidities or other characteristics that increase nephrotoxic risk that were not included in clinical trials. Although clinicians prescribe the vast

Table 1. Nephrotoxic drugs and intoxicants

- **Therapeutic medications**
  - Antimicrobial
    - *Aminoglycosides*
    - *Antiviral agents*
    - *Amphotericin B*
    - *Colistin*
    - *Polymixin B*
    - *Sulfadiazine*
    - *Quinolones*
    - *Vancomycin*
  - Chemotherapy
    - *Platins*
    - *Ifosfamide*
    - *Mitomycin*
    - *Gemcitabine*
    - *Methotrexate*
    - *Pentostatin*
    - *Interleukin-2 (high dose)*
    - *Antiangiogenesis agents*
    - *Immunotherapies (immune checkpoint inhibitors, chimeric antigen receptor T cells)*
  - Analgesics
    - *NSAIDs*
    - *Selective COX-2 inhibitors*
    - *Phenacetin*
    - *Analgesic combinations*
  - Immunosuppressives
    - *Calcineurin inhibitors*
    - *Sirolimus, everolimus*
  - Other
    - *ACE inhibitors/ARBs/renin inhibitors*
    - *SGLT-2 inhibitors (canagloflozin, dapagliflozin)*
    - *Methoxyflurane*
    - *Sucrose (IVIg excipient), hydroxyethyl starch, mannitol, dextran*
    - *Pamidronate, Zolendronate*
    - *Topiramate, Zonisamide*
    - *Orlistat*
    - *Statins*
    - *Mesalamine*
- **Alternative/health products**
  - Herbal remedies
    - *Aristolochic acid*
    - Ephedra *sp.*
    - Glycyrrhiza *sp.*
    - Datura *sp.*
    - Taxus celebica
    - Uno degatta
    - *Cape aloes*
  - Adulterants
    - *Mefenamic acid*
    - *Dichromate*
    - *Cadmium*
    - *Phenylbutazone*
    - *Melamine*
- **Diagnostic agents**
  - Radiocontrast
    - *High osmolar*
    - *Low osmolar*
    - *Iso-osmolar*
  - Other agents
    - *Gadolinium (in high dose)*
    - *Oral NaP solution (colonoscopy prep)*
- **Environmental intoxicants**
  - Heavy metals
    - *Lead*
    - *Mercury*
    - *Cadmium*
    - *Uranium*
    - *Copper*
    - *Bismuth*
  - Solvents
    - *Hydrocarbons*
  - Other toxins
    - *Silicon*
    - *Germanium*

NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclo-oxygenase; ACE, angiotensin-converting enzyme; ARBs, angiotensin-receptor blockers; SGLT-2, sodium glucose transporter-2; NaP, sodium phosphate; IVIg, intravenous immunoglobulin; sp., species.

majority of potentially nephrotoxic medications, many are also available as over-the-counter preparations. Radiocontrast agents, in particular those delivered intra-arterially at high dose, are another potential cause of AKI (22,23).

In addition to Food and Drug Administration (FDA)–approved medications, unregulated sources of potentially nephrotoxic substances are the alternative/complementary products, which are widely available at most health food stores (17–20). Included are items described as herbal remedies, natural products, and nutritional supplements (16). Another concern is that these products often contain a number of harmful chemicals and/or contaminants that are not listed on the label (16–20). Not uncommonly, the substances listed on the package label are present in varying amounts ranging from large, to small, to even nonexistent. In addition to direct nephrotoxicity, herbal products may interact with conventional drugs producing another potential avenue of nephrotoxicity. Examples of such unlisted contents include *Ephedra* species and aristolochic acid as well herbal products adulterated with phenylbutazone and other nonsteroidal anti-inflammatory drugs (NSAIDs), cadmium, and dichromate (16–20).

Drug Dose and Duration of Therapy

One of the most important parts of drug-induced nephrotoxicity is the innate kidney toxicity of the offending agent. A number of drug characteristics and their varied mechanisms of action play a role in causing kidney injury (Figure 1). High doses and prolonged courses of certain nephrotoxins will enhance risk for kidney injury *via* excessive exposure of the kidney, even in patients with minimal or no underlying risk. Several drugs such as the aminoglycosides, platinums, amphotericin B, and colistin fall into this category (24–28).

Drug Characteristics (Solubility, Structure, and Charge)

Drugs and metabolites that are insoluble in the urine may cause acute crystalline nephropathy by precipitating in distal tubular lumens (11,29–31). This process is enhanced further by reduced urinary flow rates, urine pH (depending on drug pKa), excessive drug dosing, and rapid

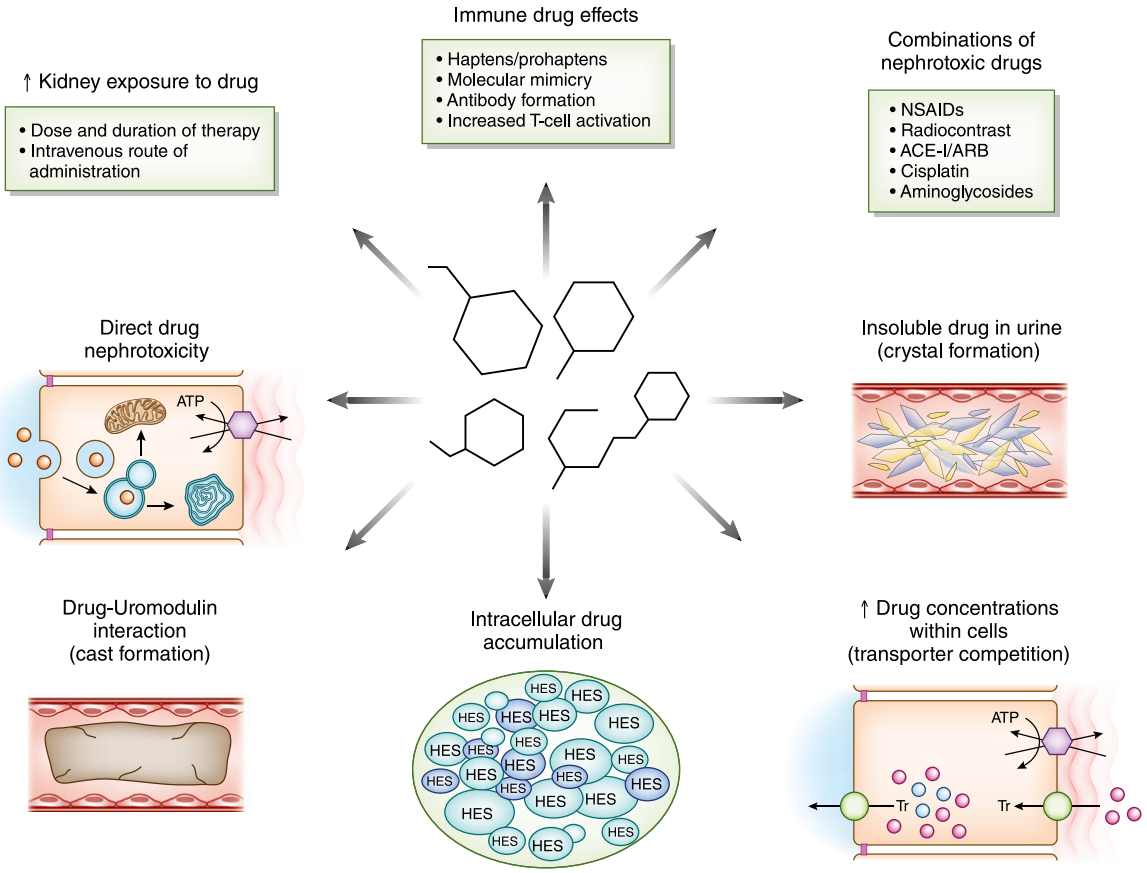

Figure 1. | **Drug factors associated with increased risk for nephrotoxicity.** Medications cause kidney injury through various mechanisms. Increased exposure of the kidney on the basis of route, dose, and duration of drug exposure; drug-related immune effects (such as B-lactams, PPIs, NSAIDs, and immune checkpoint inhibitors); combined nephrotoxic drug exposure; and drug and metabolite insolubility in the urine (such as methotrexate, acyclovir, and sulfadiazine) lead to kidney injury. In addition, increased drug concentrations within tubular cells are due to transport effects (such as tenofovir and cisplatin), intracellular accumulation of certain drugs due to lack of metabolizing enzymes (such as sucrose and hydroxyethyl starch), innate direct cell toxicity (such as aminoglycosides, colistin, and amphotericin B), and intratubular cast formation from drugs interacting with uromodulin (vancomycin). ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HES, hydroxyethyl starch; NSAIDs, nonsteroidal anti-inflammatory drugs; PPI, proton pump inhibitor; Tr, transporter.

infusion rates. In addition to obstructing urinary flow, precipitated crystals induce inflammation in the surrounding interstitium. Medications associated with development of crystalline nephropathy include methotrexate, acyclovir, indinavir/atazanavir, sulfadiazine, vitamin C, foscarnet, oral sodium-phosphate, and triamterene.

A number of medications used for intravascular volume repletion (dextran, hydroxyethyl starch) or as carrier molecules (sucrose with intravenous immunoglobuling) are associated with osmotic nephropathy (32,33). These drugs accumulate within phagolysosomes of proximal tubular cells. Because of their structure, these molecules cannot be metabolized and ultimately cause lysosomal dysfunction and cell swelling.

An interesting drug characteristic that enhances nephrotoxicity is the positive charge of polycationic aminoglycosides, which are attracted to the negatively charged proximal tubular membrane phospholipids (24,34). This facilitates drug binding to the megalin/cubilin receptor complex. For example, aminoglycoside nephrotoxicity is in part related to their cationic charge—neomycin has higher cationic charge and is more nephrotoxic than amikacin, which has a lower cationic charge.

Drug Combinations

Combinations of potential nephrotoxic drugs can increase risk for kidney injury with examples including vancomycin+piperacillin/tazobactam, aminoglycosides+cephalothin, NSAIDs+radiocontrast, and cisplatin+aminoglycosides (35–39). As will be reviewed, the pathway of excretion by the kidney represents another risk for drug nephrotoxicity. Medications compete with endogenously produced substances (and other drugs) for transport proteins and influx/efflux transporters, which can increase intracellular drug concentration and risk for kidney injury (5–7). These drug-drug interactions increase kidney injury and overall drug toxicity.

Innate Drug Nephrotoxicity. A number of medications maintain higher potential for causing kidney injury on the basis of their more significant innate nephrotoxicity. These drugs, which include the aminoglycosides, amphotericin B, the polymyxins, and cisplatin, may cause kidney injury with therapeutic doses and brief durations of exposure (5–7,40–42).

Accumulation of high concentrations of the polycationic aminoglycosides within intracellular lysosomes causes lysosomal injury, which is associated with phospholipid membrane injury, oxidative stress, and mitochondrial dysfunction. This promotes proximal tubular cell apoptosis and necrosis with clinical manifestations such as an isolated proximal tubulopathy or AKI (5–7,40–42).

Amphotericin B, and the lipid/liposomal formulations to a lesser degree, cause kidney injury by disrupting tubular cell membranes and increasing permeability to cations, which result in tubular dysfunction due to cell swelling/dysfunction (40). In general, the lipid/liposomal formulations are less nephrotoxic. The polymixin antimicrobial agents, colistin and polymyxin B, are highly nephrotoxic with a very narrow therapeutic window. Nephrotoxicity is related to their D-amino content and fatty acid component, which increases cellular membrane permeability and allows cation influx (41). This effect leads to tubular cell swelling and lysis with AKI development.

The acyclic nucleotide phosphonates (adefovir, cidofovir, tenofovir) enter the cell *via* basolateral human organic anion transporter–1(hOAT-1) and promote cellular injury primarily through disturbing mitochondrial function. Mitochondrial injury is manifested by mitochondrial enlargement, clumped cristae, and convoluted contours that impair cellular energetics (8,10,26,43). Tenofovir, which is employed widely to treat hepatitis B virus and HIV infection, is associated with proximal tubulopathy and AKI (8,10,26,43).

Antiangiogenesis therapy with monoclonal antibodies against vascular endothelial growth factor (VEGF), circulating soluble VEGF receptors, and small molecule tyrosine kinase inhibitors that impair intracellular VEGF signaling pathways are associated with various forms of kidney injury (11,44–47). In the kidney, VEGF is produced by podocytes and binds glomerular and peritubular capillary endothelial cell VEGF receptors. Glomerular endothelial VEGF receptor binding maintains normal fenestrated endothelial health and is important for normal functioning of the glomerular basement membrane (11,44–47). Reduction in VEGF levels or signaling pathways by antiangiogenic drugs promotes loss of the healthy fenestrated endothelial phenotype and promotes microvascular injury and thrombotic microangiopathy, causing proteinuria and AKI. Reduced nephrin expression in the slit diaphragms may also contribute to the development of proteinuria. Although other kidney lesions occur with these drugs, endothelial injury and thrombotic microangiopathy are most common (11,44–47). By interfering with local alternative complement pathway regulators, these drugs may also activate complement and increase risk for TMA (48).

Drug-Induced Inflammation

Another pathway of drug-induced nephrotoxicity is through induction of an inflammatory response by the host, which can target the kidney (49–53). Through multiple mechanisms (hapten/prohapten, molecular mimicry, immune-complex formation), medications can promote the development of acute interstitial nephritis (AIN) leading to AKI and/or various urinary abnormalities such as tubular proteinuria, pyuria, and hematuria (49–52). Classic drugs associated with AIN include antimicrobial agents (in particular B-lactams and sulfonamides), NSAIDs, proton pump inhibitors, and aminosalicylates (49–53). Newer agents such as the immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab) cause AIN *via* activation of T cells and perhaps reducing tolerance to exogenous drugs (54–56). As will be discussed, the patient's genetic makeup may enhance immunogenicity to exogenous agents.

Drug-Induced Cast Nephropathy

Another intriguing drug-related kidney injury is vancomycin-related obstructive tubular cast formation. Using immunohistologic staining techniques to detect vancomycin in kidney tissue, casts composed of noncrystal nanospheric vancomycin aggregates entangled with uromodulin have been observed in patients with AKI (57). In these patients, high vancomycin trough plasma levels were observed. These same vancomycin casts were reproduced experimentally in mice using *in vivo* imaging techniques. Thus, the interaction of uromodulin with nanospheric vancomycin aggregates represents a new mode of tubular injury with development of vancomycin-associated cast nephropathy (57).

The Patient

There are a number of patient-specific factors that increase risk for medication-induced nephrotoxicity (Figure 2, Table 2). Underlying risk factors for nephrotoxicity may be nonmodifiable, such as older age and female sex, which are associated with decreased lean body mass and reduced total body water that can lead to excess drug dosing (6–9). A "normal serum creatinine" in these patients may actually be a lower GFR. Women and the elderly have lower serum albumin concentrations—hypoalbuminemia results in reduced drug binding and increased free drug concentrations that can be nephrotoxic (6–9,35–38). In addition to these factors, the elderly have an increased propensity to vasoconstriction from excessive circulating angiotensin II and endothelin levels and have higher levels of oxidatively modified biomarkers (58). These factors combine to increase patient exposure to excess drug concentrations and nephrotoxicity risk.

Genetic Makeup

Along the lines of nonmodifiable risk factors is the patient's underlying genetic makeup. In fact, the role of pharmacogenetics as an explanation for the heterogeneous patient response to drugs (underdosing, therapeutic dosing, and overdosing) reflects genetic makeup and supports the need for "personalized" or "precision" medicine. As such, underlying host genetic makeup can enhance vulnerability of the kidney to potential nephrotoxins (59–63). There are data that suggest that metabolic pathways, transport proteins, and drug transporters vary between patient populations due to the effect of genetic composition. Several enzymes that comprise the hepatic cytochrome P450 (CYP450) enzyme system have gene polymorphisms that are associated with reduced drug metabolism and subsequent end organ toxicity. Because the kidney also possesses CYP450 enzymes that participate in drug metabolism (59–63), it is not surprising that gene polymorphisms favoring reduced drug metabolism could increase nephrotoxic risk.

Polymorphisms of genes encoding proteins involved in the metabolism and subsequent elimination of drugs by the

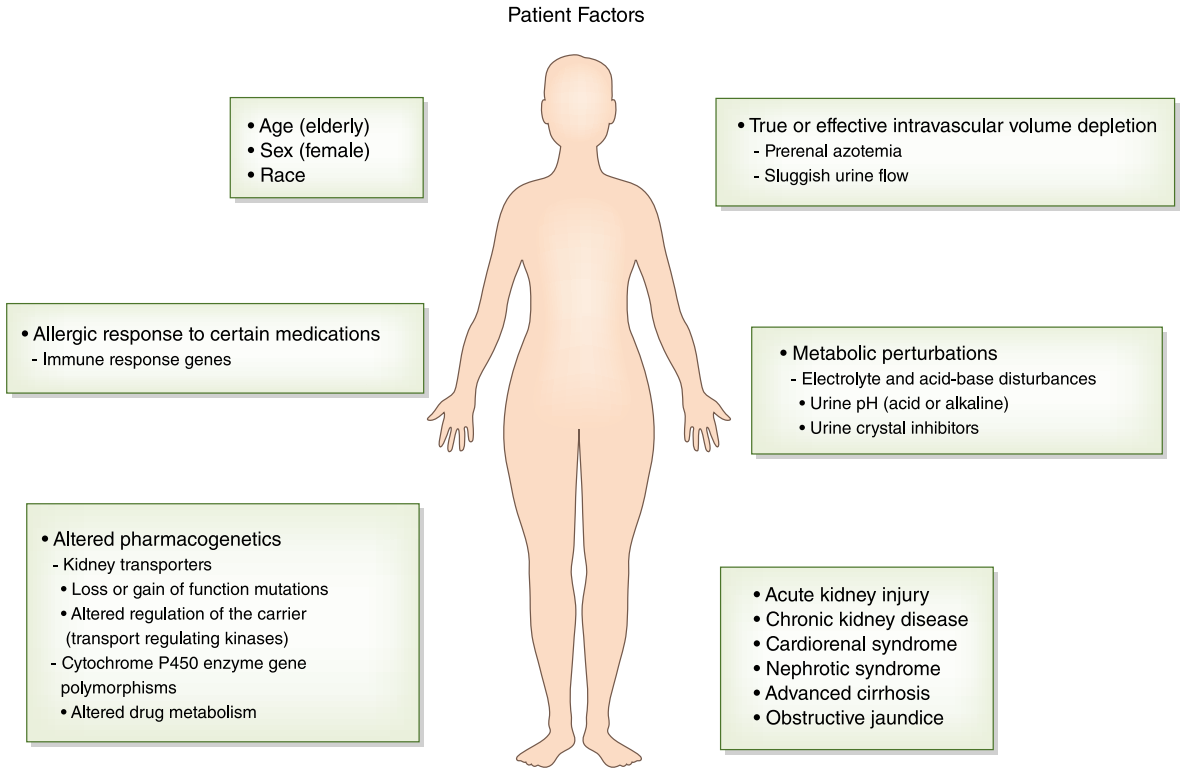

Figure 2. | **Patient factors that increase risk for drug-induced nephrotoxicity.** Patients have risk factors from nonmodifiable characteristics such as age, sex, race, and the genetic makeup of immune response genes and drug metabolizing enzymes and transport pathways that enhance the nephrotoxicity of drugs. Comorbid conditions such as liver disease, heart disease, and CKD and acutely developed diseases such as intravascular volume depletion, metabolic perturbations, and AKI are also important risk factors for drug-induced nephrotoxicity.

kidney as well as the repair pathways after drug injury are correlated with various levels of drug sensitivity. Polymorphisms in genes encoding ERCC1, a key enzyme in the DNA repair pathway by which cells repair platinum-induced DNA damage, may be associated with increased nephrotoxicity (64). Polymorphisms in cytosolic glutathione-S-transferase enzymes, which normally function to detoxify reactive molecules such as cisplatin, increase risk for nephrotoxicity with exposure to this drug (65).

Loss-of-function mutations in apical secretory transporters that reduce drug efflux from the cell into the urine, and mutations in kinases that regulate drug carrier proteins, can impair drug elimination and promote nephrotoxicity by elevating intracellular drug concentrations (59–63). It is probable that patients differ in the function and regulation of receptors, channels, carriers, and transporters that regulate the metabolism and elimination of drugs by the kidneys. Tenofovir-induced Fanconi syndrome represents one such example (66). Patients with HIV receiving tenofovir who developed Fanconi syndrome were noted to have a single nucleotide polymorphism: 1249 G→A single nucleotide polymorphism in the gene coding the multidrug-resistant protein-2 efflux transporter, which transports tenofovir out of the cell into the urine. In contrast, treated patients with HIV who did not develop Fanconi syndrome did not have the gene polymorphism (66).

Genetic alterations in a patient's immune system may also enhance risk for drug nephrotoxicity *via* inflammatory injury. The administered drug or its metabolite may form adducts that modify their physical structure, which enhances their immunogenicity (49,53). Heterogeneity in patient response to drugs and exogenous agents exists, with one example being the heightened allergic response of some individuals as compared with others. As such, differences in innate host immune response genes can predispose some patients to developing an allergic reaction to a medication (49,53). In fact, the variability of immune responses has been demonstrated in patients who develop drug-induced AIN, which appears to be a T cell–driven process (49). Thus, enhanced vulnerability to an allergic response in the kidney and the associated development of AIN reflect yet another form of drug nephrotoxicity.

Comorbid Diseases

Underlying AKI and CKD are also important risk factors for increasing vulnerability to nephrotoxic injury (6–9, 35–37). The decline in GFR and increase in tubular secretion of endogenous substances (and medications) increase risk for adverse drug-related kidney effects. GFR reduction can also result in excessive drug dosing for medications excreted by the kidneys, increased drug exposure in a reduced number of functioning nephrons and ischemia preconditioned tubular cells, and more robust oxidative injury response to various medications by the kidney. In addition, increased tubular secretion of drugs that are cleared by both glomerular filtration and tubular secretion may enhance kidney tubular toxicity (6–9).

Table 2. Risk factors for drug nephrotoxicity

Drug factors
Prolonged dosing periods and nephrotoxic drug exposure
Potent direct nephrotoxic drug effects
Combinations of toxins/drugs promoting enhanced nephrotoxicity
Competition between endogenous and exogenous toxins for transporters, increasing drug accumulation within the tubular cell
Insoluble drug and/or metabolite with intratubular crystal precipitation
Drug that accumulates in lysosome due to lack of enzymes to metabolize the drug
Patient factors
Female sex
Old age (>65 yr of age)
Nephrotic syndrome
Cirrhosis/obstructive jaundice (nephrotoxic bile acids)
AKI
CKD
True or effective volume depletion (kidney hypoperfusion)
Decreased GFR
Enhanced proximal tubular toxin reabsorption
Sluggish distal tubular urine flow rates
Metabolic perturbations
Hypokalemia, hypomagnesemia, hypercalcemia
Alkaline or acid urine pH
Immune response genes increasing allergic drug response
Pharmacogenetics favoring drug toxicity
Gene mutations in hepatic and kidney P450 system
Gene mutations in kidney transporters and transport proteins
Kidney factors
High rate of blood delivery to the kidneys (approximately 25% of cardiac output)
Increased drug concentrations within the kidney medulla and interstitium
Biotransformation of drugs to nephrotoxic metabolites and reactive oxygen species
High metabolic rate of tubular cells (*i.e.*, loop of Henle) within a hypoxic environment
Proximal tubular uptake of drugs
Apical drug uptake via *endocytosis or pinocytosis with drug accumulation*
Basolateral drug transport via *hOAT or hOCT with drug accumulation*
Reduced drug efflux via *apical transporters with drug accumulation*

hOAT, human organic anion transporters; hOCT, human organic cation transporters.

Other types of systemic and kidney disease may also increase the nephrotoxic effects of drugs. Nephrotic syndrome and cirrhosis enhance nephrotoxic risk through multiple mechanisms that include altered kidney perfusion from reduced effective circulating blood volume, hypoalbuminemia with increased free circulating drug levels, and unrecognized kidney impairment (6–9,35–38). Obstructive jaundice also enhances toxicity to certain drugs, such as the aminoglycosides, through altered hemodynamics such as decreased renal blood flow and direct toxic effects of bile salts on tubular epithelia (67). True volume depletion from vomiting, diarrhea, and diuretics as well as effective volume depletion associated with congestive heart failure, ascites, and sepsis increase risk for drug nephrotoxicity. Induction of kidney hypoperfusion and prerenal physiology by these comorbidities increases the nephrotoxicity of many drugs (6–9,35–38). Ultimately, reduced kidney perfusion enhances nephrotoxicity in drugs excreted through the kidneys by fostering drug overdosing, increasing drug concentrations within tubular cells in drugs reabsorbed by the proximal tubule, and enhancing drug/metabolite crystal precipitation within distal tubular lumens in the setting of sluggish urinary flow rates of insoluble drugs (6–9,35–38).

Metabolic Disturbances

A number of metabolic abnormalities can also increase risk for adverse kidney effects with certain drugs. For example, electrolyte disorders such as hypokalemia, hypomagnesemia, and hypocalcemia increase the nephrotoxicity associated with the aminoglycosides (6–9,35–38,68). Severe hypercalcemia leads to afferent arteriolar vasoconstriction and tubular sodium and water wasting, which induces prerenal physiology, which enhances nephrotoxic drug injury. Metabolic disorders that alter urinary pH also increase risk for intratubular crystal deposition with certain drugs (6–9,29–31,68). Systemic metabolic acidosis or alkalosis may decrease or increase urine pH, whereas proximal and distal renal tubular acidoses are associated with alkaline urine due to impaired ability of the kidney to excrete H^+ ion. Acidic urinary pH (<5.5) increases intratubular crystal deposition with drugs such as sulfadiazine, methotrexate, and triamterene that have limited solubility in a low-pH environment (11,25–27). Alkaline urine (pH>6.0) increases crystal precipitation within tubular lumens from drugs such as indinavir, atazanavir, oral sodium phosphate solution, and ciprofloxacin (10,11,21,29–31). In addition, drugs such as topiramate, zonisamide, and acetazolamide induce the formation of an alkaline urine by inhibiting carbonic anhydrase thereby promoting precipitation of calcium-phosphate within tubules and enhancing risk for nephrolithiasis (30,31).

The Kidney

The mechanism by which the kidney metabolizes and excretes various drugs and toxins importantly contributes to drug nephrotoxicity (Figure 3). The high rate of drug and toxin delivery to the kidney, a result of high renal blood flow, which approximates 25% of cardiac output, exposes the kidney to significant drug concentrations (6–9). In addition, many tubular cells, particularly those in the loop of Henle, reside in a relatively hypoxic environment due to the high metabolic requirements associated with active solute transport by Na^+-K^+-ATPase–driven transport (6–9,68,69). Excessive cellular workload of these cells in this relatively hypoxic environment enhances risk for a nephrotoxic-related injury. High concentrations of certain medications and their metabolites develop in the kidney medulla and interstitium from the enormous concentrating ability of the kidney, which can induce kidney injury through direct toxicity as well as ischemic damage from reduced prostaglandin and increased thromboxane production (6–9,68,69).

Drug Metabolism

In addition to hepatic metabolism, a number of drugs undergo biotransformation by kidney enzyme systems, including the CYP450 and flavin-containing monooxygenases

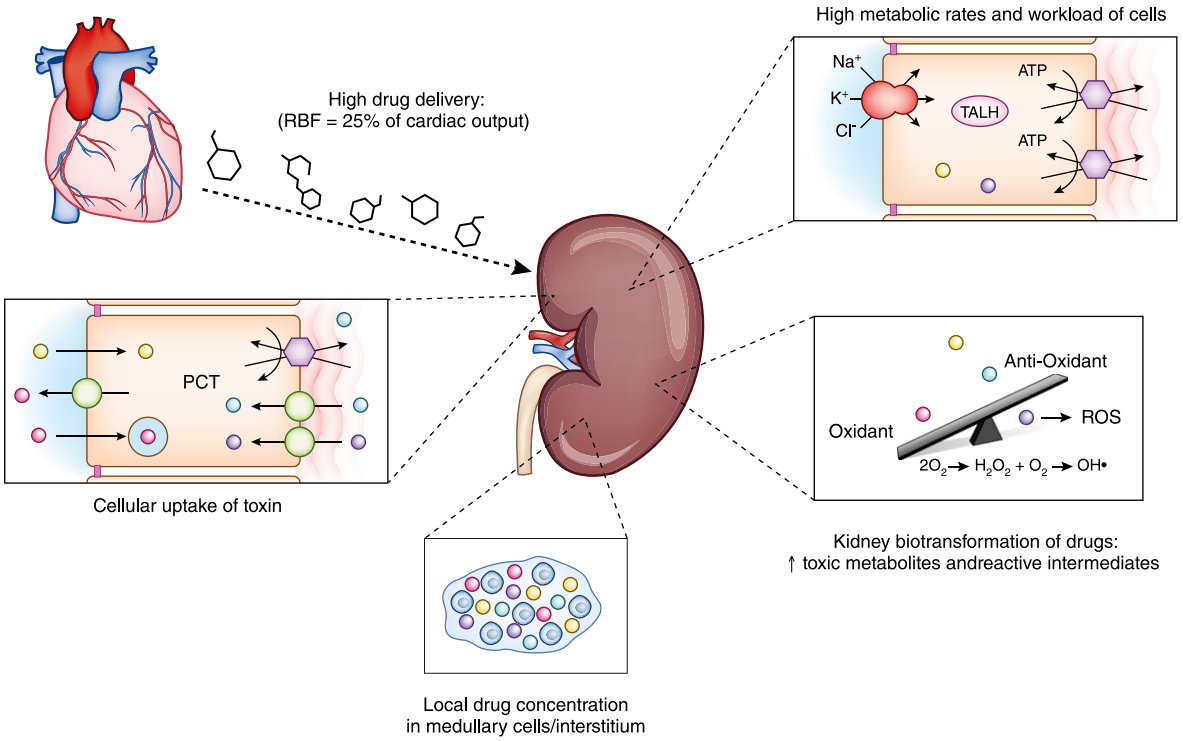

Figure 3. | **Kidney factors that enhance risk for drug-induced nephrotoxicity.** High RBF increases drug delivery and exposure to the kidney. High metabolic rates of TALH tubular cells increase risk for drug nephrotoxicity. Kidney metabolism of drugs to toxic metabolites and ROS overwhelms local antioxidants and promotes tubular injury. Increased concentrations of potentially nephrotoxic drugs in the medulla and interstitium increase kidney injury. Apical uptake of certain drugs (aminoglycosides, hydroxyethyl starch) and basolateral transport of drugs through the organic anion transporter (tenofovir) and organic cation transporter (cisplatin) increase kidney toxicity. PCT, proximal convoluted tubule; RBF, renal blood flow; ROS, reactive oxygen species; TALH, thick ascending loop of Henle.

(6–9,68–71). This leads to the potential formation of nephrotoxic metabolites and reactive oxygen species as seen with the aminoglycosides, platinums, and several other medications (6–9,34,68–74). These byproducts of biotransformation may swing the balance in favor of oxidative stress, which outstrips natural antioxidants and increases kidney injury *via* DNA strand breaks, nucleic acid alkylation or oxidation, lipid peroxidation, and protein damage (6–9,34,68–74).

Drug Excretory Pathway

Drugs are excreted from the body by both glomerular filtration and tubular secretion. An important avenue of kidney injury occurs with excretion of drugs *via* the active transporters in proximal tubular cells (6–9,75–79). Extensive tubular cell uptake of potential nephrotoxic drugs *via* both apical and basolateral transport systems underlies development of kidney injury. From the urinary space, apical uptake of drugs occurs *via* endocytosis/pinocytosis and other active/passive transport pathways (6–9,32–34). Medications taken up *via* this pathway include polycationic aminoglycosides (Figure 4A), heavy metals, and various complex sugars and starches. In the case of aminoglycosides, after endocytic receptor (megalin/cubilin) binding and uptake of these cationic ligands, these drugs are translocated into the lysosomal compartment where they accumulate and subsequently form myeloid bodies (6,34,68,69). Myeloid bodies are membrane fragments and damaged organelles formed as a consequence of aminoglycoside inhibition of lysosomal enzymes. This apical pathway of uptake leads to accumulation of a critical concentration of aminoglycoside within cells, which triggers an injury cascade leading to cell injury and death, which present clinically as a proximal tubulopathy and/or AKI. Filtered dextran, sucrose, and hydroxyethyl starch may cause tubular injury when they undergo pinocytosis by proximal tubular cells (6,9,34,35). Similar to the aminoglycosides, after pinocytosis these substances are taken up by and collect in lysosomes (Figure 4B). The absence of cellular enzymes capable of metabolizing these substances allows them to build up within the cytoplasm and cause tubular cell injury and AKI (6,9,34,35).

In addition to apical uptake of drugs, another pathway of proximal tubular cell drug exposure occurs *via* basolateral delivery *via* the peritubular capillaries (6,26,43,72–76). After delivery of potentially nephrotoxic drugs by the peritubular capillaries, uptake into proximal tubular cells occurs *via* a family of active transporters (6,26,43,72–76). These include the hOAT for negatively charged drugs and the human organic cation transporters (hOCT) for positively charged drugs (6,26,43,72–76). Endogenously produced anionic and cationic substances, as well as exogenously administered drugs, compete for transport *via* these pathways. Classic examples of potentially nephrotoxic drugs utilizing these transport pathways are the acyclic nucleotide phosphonates such as tenofovir (Figure 5A), which are transported *via* hOAT-1 (6,26,43), and cisplatin, which is transported *via*

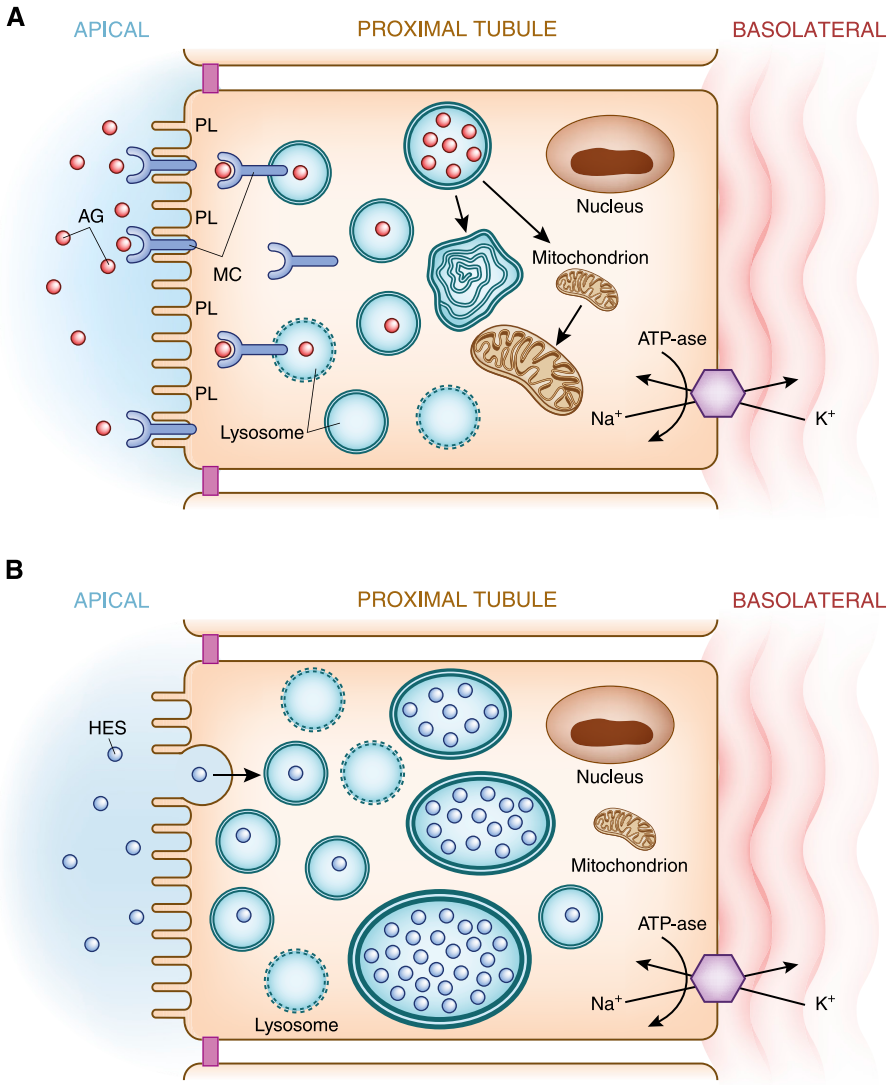

Figure 4. | **Apical transport of drugs in the proximal tubule.** (A) Aminoglycosides Apical membrane handling of substances, in this example aminoglycosides, by proximal tubular cells increases cellular uptake of this nephrotoxic drug. Polycationic aminoglycosides are attracted to the anionic phospholipid membranes where they interact with megalin-cubilin receptor on the apical surface. The aminoglycosides are endocytosed and enter the cell where they are translocated into lysosomes. Lysosomal injury and rupture along with mitochondrial injury result in tubular cell injury. (B) Hydroxyethyl starch. Apical membrane handling of hydroxyethyl starch by proximal tubular cells increases cellular uptake of this potentially nephrotoxic drug. Hydroxyethyl starch as well as sucrose (carrier for IVIg), dextran, and mannitol undergo pinocytosis and enter the cell where they are translocated into lysosomes. The lack of enzymes necessary to metabolize these substances allows accumulation within lysosomes, which causes cell swelling (occluding tubular lumens) and eventual lysosomal rupture resulting in tubular cell injury. AG, aminoglycosides; HES, hydroxyethyl starch; IVIg, intravenous immunoglobulin; K^+, potassium; MC, megalin-cubilin; Na^+, sodium; PL, anionic phospholipids.

hOCT-2 (Figure 5B) (72–74,76). Upon transport of drugs into proximal tubular cell cytoplasm, they move through the intracellular space by various regulated carrier proteins, and subsequently exit from cells *via* apical transport proteins (5,6,26,43,72–74,76). Transport of drugs through proximal tubular cells, as well as the buildup of drug concentrations when transport out of cells is blunted (or transport into the cell is increased), enhances risk for nephrotoxicity (6,9,26,43,72–74,76). Examples of the former are loss-of-function mutations in and competition for apical secretory transporters (6,9,26,43,66,72–74,76). This reduces nephrotoxin efflux from cell into urine, which may promote accumulation of toxic substances within proximal tubular cells and cause cellular injury *via* apoptosis or necrosis (Figure 5). An example of the latter is reduced glomerular filtration of drug, which increases proximal tubular drug secretion and increases tubular cell drug exposure (6–9). Ultimately, this extensive trafficking of drugs increases tubular exposure and risk for elevated concentration of potentially nephrotoxic drugs when other risk factors supervene.

Preclinical and Clinical Tests for Drug-Induced Nephrotoxicity

Kidney-on-a-chip technology is being employed in the drug discovery field using *in vitro* models that mimic kidney

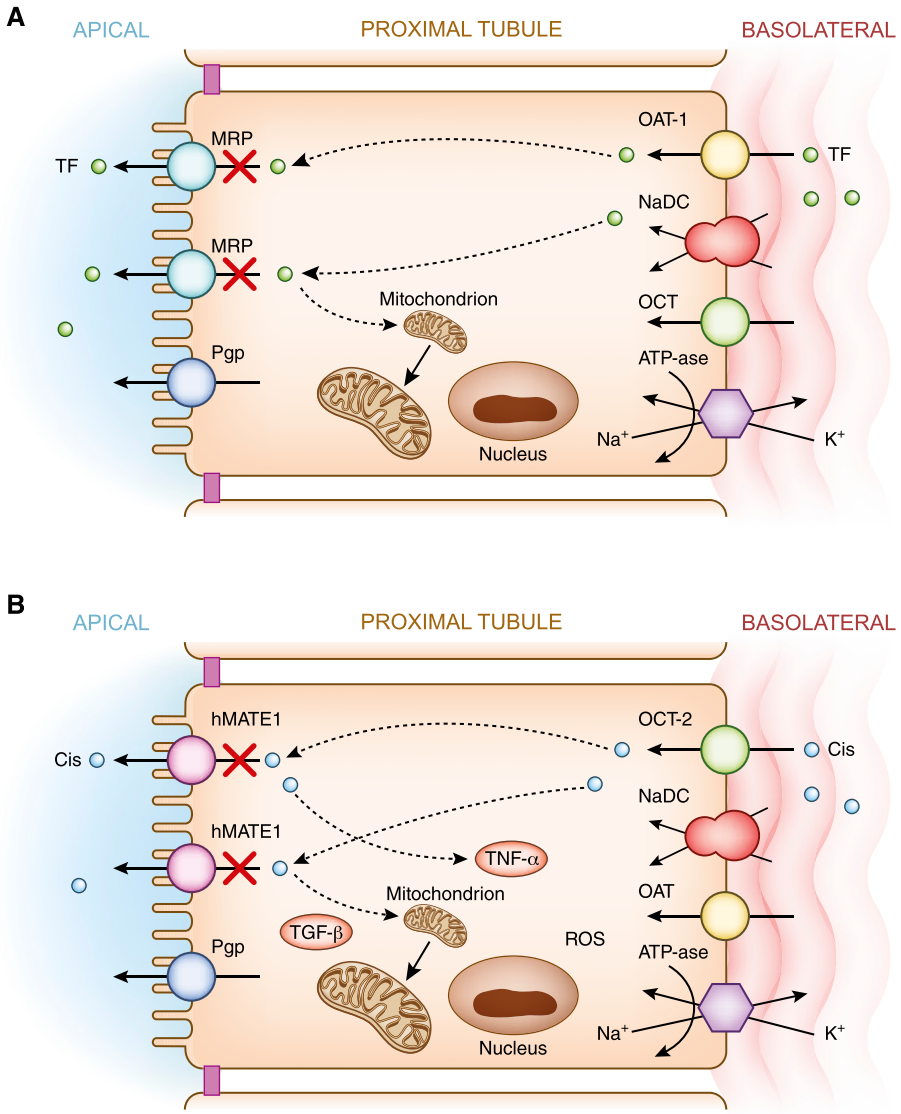

Figure 5. | **Basolateral transport of drugs.** (A) Tenofovir. Basolateral handling of certain drugs, in this example tenofovir, by proximal tubular cells may lead to cellular injury. Tenofovir is delivered to the basolateral membrane, transported into the cell *via* the human organic anion transporter-1, and excreted by various apical transporters into the urinary space. In this example, transport by the multidrug-resistance protein transporters is inhibited or dysfunctional, causing intracellular accumulation of drug and nephrotoxicity *via* mitochondrial toxicity. (B) Cisplatin. Basolateral handling of certain drugs such as cisplatin by proximal tubular cells may lead to cellular injury. Cisplatin is delivered to the basolateral membrane, transported into the cell *via* the human organic cation transporter-2, and excreted by various apical transporters into the urinary space. Intracellular accumulation of cisplatin due to increased basolateral uptake or deficient efflux by the hMATE1 transporters into the urine leads nephrotoxicity *via* production of a number of substances (TNF-α, TGF-β, and ROS), which promote mitochondrial toxicity. Cis, cisplatin; hMATE1, human multidrug and toxin extrusion protein transporter; K^+, potassium; MRP, multidrug resistance protein transporter; Na^+, sodium; NaDC, sodium dicarboxylate transporter; OAT-1, organic anion transporter-1; OCT-1, organic cation transporter-1; Pgp, P-glycoprotein transporter; ROS, reactive oxygen species; TF, tenofovir; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor α.

physiologic structures and continuous flow conditions (74,80,81). Most systems consist of kidney tubular epithelial cells embedded on the surface of an extracellular matrix, which is attached to perfusable microchannels that allow for nutrient enrichment, waste clearance, and flow (81). These *in vitro* models, in particular the 3D models, are thought to more reliably replicate the *in vivo* environment and predict nephrotoxicity that occurs with certain drugs in the clinical setting (81). Proximal tubular cells cultured under these physiologic conditions demonstrate various markers of drug cytotoxicity. Kidney-on-a-chip models have been successfully employed with known nephrotoxins such as cisplatin (74).

Novel biomarkers of injury are also useful to examine for the possibility of structural kidney injury due to various drugs. To this point, the FDA and European Medicines Agency (EMEA) approved seven novel kidney biomarkers, along with traditional clinical chemistry and histopathology, for preclinical animal studies to detect nephrotoxicity in the development of new drugs (82). Biomarkers were

added to preclinical studies on the basis of their superior sensitivity and specificity in detecting drug-induced nephrotoxicity as compared with traditional tests. Because these biomarkers detect injury in various parts of the nephron, they would be well suited not only to signal the occurrence of parenchymal kidney injury, but also point to the site of injury. Thus, animal experiments measuring these biomarkers after administration of a medication under development would provide insight into potential nephrotoxicity. In addition to drug development, the FDA and EMEA recommend that biomarkers should eventually be evaluated for their utility in clinical studies to promote patient safety and guide therapeutic clinical decisions (83). Novel biomarkers could also be measured in stored urine samples from patients participating in clinical trials studying the efficacy and safety of various drugs. The results of animal and human studies would provide a potential avenue to identify drug-induced structural kidney injury and allow recognition of drug-induced nephrotoxicity at earlier time points to allow drug discontinuation before further kidney injury occurs. Kidney-on-a-chip technology in combination with the urine microscopy (84) and novel biomarkers may allow clinicians to better understand if a drug is nephrotoxic and, if so, the site of injury and mechanism underlying development of kidney injury.

Summary

Medications are widely prescribed and ingested by patients and remain a relatively common cause of kidney injury. Drug nephrotoxicity is a complicated process that involves a combination of factors including the innate nephrotoxicity of drugs, underlying patient characteristics that enhance their risk for kidney injury, and the metabolism and excretion of the potential offending agent by the kidney.

Disclosures

None.

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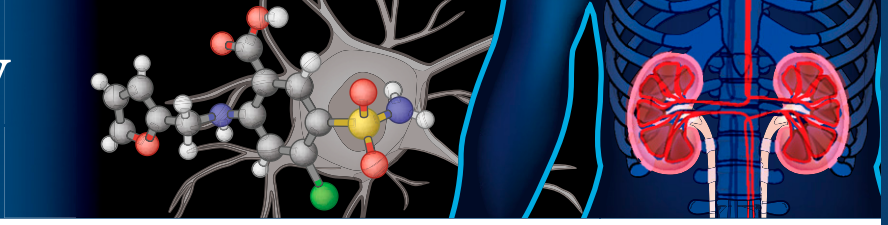

Utility of Electronic Medical Record Alerts to Prevent Drug Nephrotoxicity

Melissa Martin[1] *and F. Perry Wilson*[1,2]

Abstract

Nephrotoxin-induced AKI is an iatrogenic form of AKI that can be potentially avoided or ameliorated by prompt recognition and appropriate prescriber actions. Drug-targeted alerts, either for patients at risk of AKI or patients with existing AKI, may lead to more appropriate drug dosing and management and improved clinical outcomes. However, alerts of this type are complicated to create, have a high potential for error and off-target effects, and may be difficult to evaluate. Although many studies have shown that these alerts can reduce the rate of inappropriate prescribing, few studies have examined the utility of such alerts in terms of patient benefit. In this review, we examine the current state of the literature in this area, identify key technical challenges, and suggest methods of evaluation for drug-targeted AKI alerts.

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Introduction

AKI is a frequent complication of hospitalizations and introduces a number of challenges with regard to medication administration and dosing (1–4). Depending on the definition of "nephrotoxin," the prevalence of nephrotoxin exposure in hospitalized patients may exceed 75% (5,6), a significant statistic given that each exposure to a nephrotoxic agent increases a patient's odds of developing AKI by 53% (7). Among patients who develop AKI, approximately 20% of cases are thought to be due to nephrotoxin exposure (8–10). Furthermore, despite international guidelines for the appropriate management of AKI, which focus on cessation and avoidance of nephrotoxins, physicians frequently fail to stop nephrotoxic medications or dose adjust kidney-cleared medications as kidney function worsens (11–13). In an effort to attenuate these issues, quality control and clinical research efforts have examined the utility of targeted alerts to modify provider behavior and improve patient outcomes. Herein, we discuss the challenges in developing, implementing, and evaluating these alerts.

Conceptual Framework

The efficacy of an AKI alert is dependent on multiple inter-related factors as schematized in the conceptual model in Figure 1. Alerts are least effective when a provider is already aware of the clinical situation being alerted (endogenous recognition) or when the alert is not actionable (*e.g.*, there are no alternative therapies available). Conversely, alerts may be most effective when providers are unaware of AKI (*e.g.*, in situations where the creatinine is rising slowly) or when actionable steps are immediately evident.

Several studies have shown the potential efficacy of alerts in the hospital setting (14–16); however, extensive reviews of the clinical decision support literature have consistently described specific elements that increase provider adherence and thus, the likelihood of alert success (17–20). These factors include the speed of the information system, timing of the alert (real time and at the point of care), minimal disruption of and integration into provider workflow, simplicity and clarity of the message, and provision of references and sufficient information within the alert. One study showed the positive effects of incorporating more user-friendly changes into a creatinine clearance alert system designed to reduce prescribing errors (21). The authors incorporated educational information, added links to additional laboratory information, and changed the timing of the alert to proximate the point of medical decision making, resulting in 43% fewer prescribing errors compared with the original alerts when tested by physicians in mock clinical scenarios.

Critical aspects to improve alert efficacy are continual monitoring of decision support system performance and collection of feedback from its users, which have shown that user acceptance, perception, and confidence in the support system are prominent causes of frequent alert over-ride. One study that surveyed clinician perceptions after use of an early warning and response system for severe sepsis reported a change in patient management in about 50% of all patients as a result of the alert, while only about one third of users described the alert as useful (22). Feedback from providers suggested that such low acceptance stemmed from possible low specificity of the alert, because they perceived most alerted patients to be stable at the time of the alert and were able to more quickly recognize illness as a result of the alert in only a few patients. Similarly, a study gathering clinician perceptions of an automated

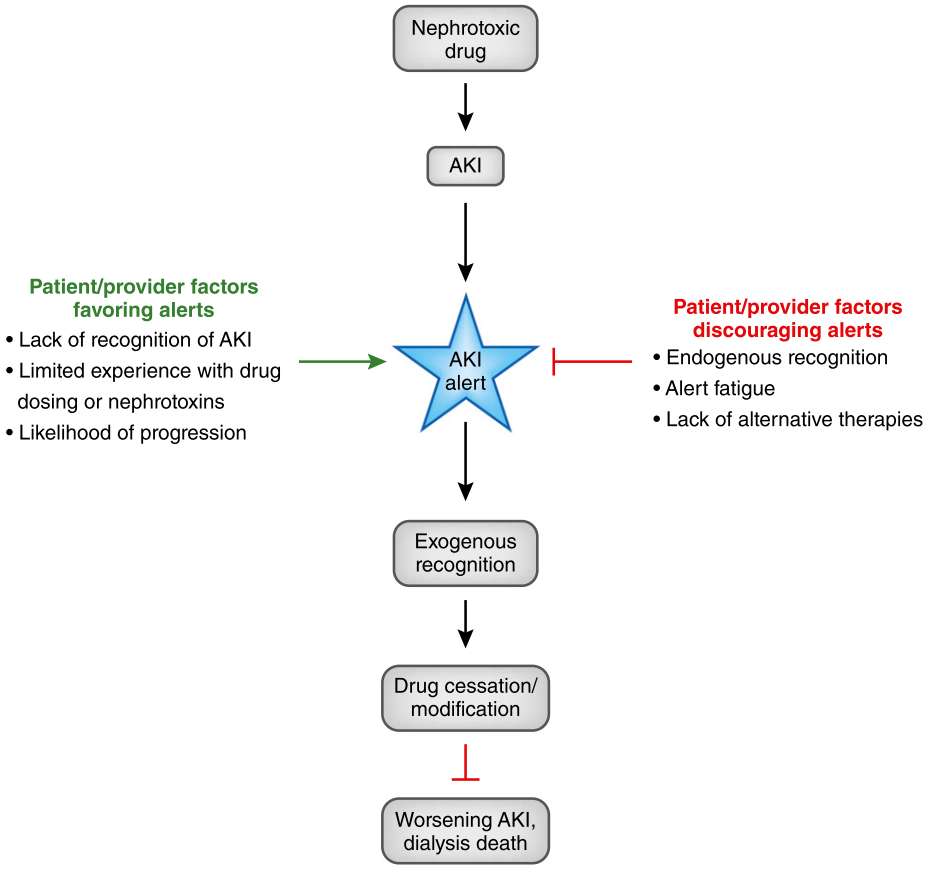

Figure 1. | **A conceptual model for the efficacy of AKI alerts highlights that an alert's success is dependent on both patient and provider factors.** Those represented by the green arrow are factors that would favor implementation of an alert system by providing scenarios where alerts may increase the ability of providers to recognize specific conditions and take immediate actions to improve patient prognosis. Those represented by the red arrow are factors that would discourage adoption of an alert system. If providers are already aware of a condition or if no actionable alternatives are available, alert fatigue may reduce efficacy of not only the alert in question but also, other clinically important alerts.

drug alert within a provider order entry system showed that, despite high potential for increased physician recognition of drug interactions, over one half of the surveyed clinicians perceived the poor signal-to-noise ratio as a significant barrier to their use (23). Shah *et al.* (24) attempted to address this issue by designing more selective alerts for ambulatory drug contraindications as a means to improve clinician acceptance. Computerized alerts were designed for selected drug contraindications that were deemed of highest clinical relevance. Alerts were then divided into disruptive alerts (requiring a provider action) for contraindications with the highest clinical severity and nondisruptive alerts (accounting for 71% of all alerts and displaying on top of the computer screen with minimal clinician interruption). Consequently, user acceptance of the more intrusive alert was 67%, an increase over previously published results in similar settings. Of course, this risks under alerting, and continual provider feedback is necessary to create an optimal balance of user acceptance and appropriate alert frequency.

Potential Harms of Alerting

Although alerts are commonly considered low-risk interventions, three potential harms are worth mentioning. First is the development of alert fatigue, a condition of decreased attention to alerts due to the proliferation or frequency of alerting (25–28). An alert, in the setting of nephrotoxin exposure, should increase "exogenous" recognition of the clinical scenario (recognition due to forces outside of the provider's own mind). In contrast, a capable provider may be likely to have endogenous recognition of the importance of the clinical scenario in the absence of the alert. Alert fatigue is more likely when endogenous recognition and exogenous recognition are in conflict (*i.e.*, an alert occurs for a condition of which a provider is already aware). Additionally, alert fatigue can occur due simply to the proliferation of alerts, even if they are informative (20,29,30). This is well documented in the intensive care unit, where frequent chimes, buzzers, and beeping fade quickly into background obscurity. Alert fatigue can be particularly insidious, because the proliferation of new alerts for different conditions can affect old alerts that were once proven to be successful. This argues for not only robust assessment of practical and clinical alert efficacy, but also, reassessment over time to ensure that alerts are still functioning as intended. Moreover, we should be comfortable discontinuing alerts, even if they are informative or have become "standard of care," should they fail to continue to show a clinical benefit.

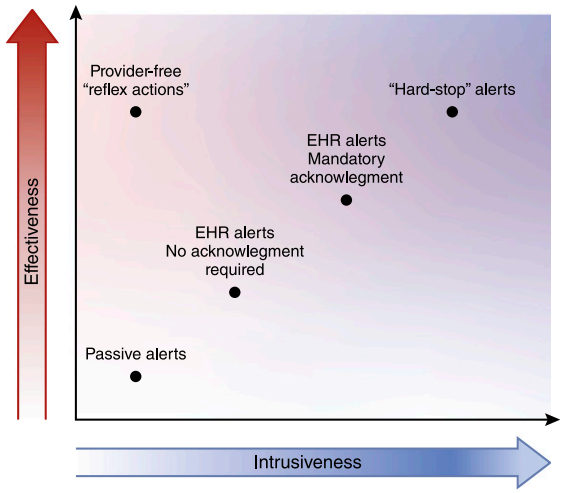

Figure 2. | Alert effectiveness is strongly related to the degree with which it intrudes on usual processes of care, creating a conflict in terms of clinical outcomes. EHR, electronic health record.

The second potential harm from alert systems is the risk of inattention to nonalerted patients. A highly effective alert reminding a physician that a certain drug should be redosed in a patient with AKI may lead that physician to believe that he or she will be alerted for all drugs that need to be redosed in a patient with AKI, leading to increased harms from those other agents. This may be difficult to measure, because often, studies may only look at the harms from the drug of interest rather than other agents to which a patient may be exposed.

Third, alerts may be categorized as "soft stop" alerts or "hard stop" alerts. A "soft stop" alert conveys a potential safety issue with existing alternatives but with no required action or acknowledgment from the provider. However, these hold a greater likelihood of being overlooked due to reasons, such as alert fatigue, as described above. (31,32) "Hard stop" alerts, which require a provider to get special approval to continue a drug, may be highly effective at decreasing the use of the drug, but they may elicit unintended adverse consequences and thus, may not be the best choice for all patients. In a randomized trial evaluating a "hard stop" rule for the coadministration of trimethoprim-sulfamethoxazole and warfarin, researchers found a dramatic 88% decrease in patients given both drugs. However, the study was stopped early because of four adverse events—two patients had a significant delay of therapy of trimethoprim-sulfamethoxazole, and two patients had a significant delay of therapy with warfarin when the alert essentially over-rode physician judgement regarding the importance of immediate treatment. This is especially applicable to patients with AKI, because nephrotoxic agents, such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and a variety of antibiotics, are frequently prescribed in elderly and critically ill patients. Although rare, significant risk exists for underdosing or complete avoidance of necessary medications, which may lead to potentially fatal therapeutic failure as shown by a case in which one patient with AKI received fatally subtherapeutic dosing of antibiotic

Potential benefits of an EMR alert system

- Reduction in medication errors (i.e. drug drug interactions, over- and underdosing)
- Early identification and appropriate treatment of underrecognized conditions
- Enhanced quality of care
- Improved patient safety and outcomes

Potential harms of an EMR alert system

- Risk for development of alert fatigue among providers (due to poor clarity, low specificity, low sensitivity, high frequency, disruption of workflow), leading to decreased attention to clinically important alerts
- Increased inattention to non-alerted patients due to increased reliance on the alert system
- Unintended adverse consequences when alerting overrides physician judgement

Limitations of an EMR alert system

- Potential for false positive alerts which may undermine alerting and reduce provider adherence
- Alert criterion may serve as poor proxies for true disease progression (i.e. eGFR in kidney disease)
- Difficulty of direct integration of alerts into the EHR system
- Possible lack of generalizability of alerts to different care settings with varied practices and patient populations

Figure 3. | Benefits, disadvantages, and limitations of an electronic medical record (EMR) alert system. A broader discussion of each is in the text.

Table 1. Summary of selected studies of drug alerts in patients with CKD and patients with AKI (43,44)

Study	Title	Study Participants	Duration
Hospitalized patients with CKD			
Chertow *et al.* (12)	Guided medication dosing for inpatients with renal insufficiency	7490 Patients in a single tertiary care hospital	Four consecutive 2-mo intervals
Nash *et al.* (37)	Reducing excessive medication administration in hospitalized adults with renal dysfunction	Adult inpatients with impaired kidney function at a 1171-bed academic medical center	Baseline data collection: 7 wk; alert (intervention) data collection: 10 wk
Galanter *et al.* (38)	A trial of automated decision supp0ort alerts for contraindicated medications using computerized physician order entry	233 Patients at a single tertiary care hospital	14 mo after alert implementation
Bhardwaja *et al.* (44)	Improving prescribing safety in patients with renal insufficiency in the ambulatory setting: The Drug Renal Alert Pharmacy (DRAP) program	6125 Adult patients in an integrated health care system with estimated creatinine clearance of 5 ml/min or lower and not receiving dialysis	15 mo
Terrell *et al.* (43)	Computerized decision support for medication dosing in renal insufficiency: A randomized, controlled trial	42 Physicians in an academic emergency department randomized to either intervention or control group	2 yr
Hospitalized patients at risk of AKI			
Goldstein *et al.* (39)	A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury	1749 Noncritically ill hospitalized children in a quaternary pediatric inpatient hospital receiving intravenous aminoglycoside or more than three nephrotoxins	3 yr, 7 mo
Hospitalized patients with AKI			
McCoy *et al.* (41)	A computerized provider order entry intervention for medication safety during acute kidney injury: A quality improvement report	1598 Adult inpatients in an academic tertiary care facility with a minimum 0.5-mg/dl increase in serum creatinine over 48 h after an order of one of 122 nephrotoxins or medications excreted by the kidneys	1 yr, 8 mo
Roberts *et al.* (42)	Clinical decision support implemented with academic detailing improves prescribing of key renally cleared drugs in the hospital setting	300-Bed teaching hospital	5 mo

Table 1. (Continued).

Control	Intervention	Measure of Efficacy	Key Results
Usual computerized order entry system	Real time computerized decision support system for prescribing drugs in patients with kidney insufficiency coupled with computerized order entry system	Rates of appropriate prescription (dose, frequency), length of stay, hospital and pharmacy costs, changes in kidney function	A computerized decision support system increased the number of appropriate prescriptions versus the computerized order entry system alone by both dose (67% in the intervention group versus 54% in the control group; $P<0.001$) and frequency (59% intervention; 35% control)
Usual care	Computerized alert system for pharmacists to identify hospitalized patients who had medications requiring dose adjustments in the setting of kidney insufficiency coupled with pharmacist feedback	Percentage of medications dosed in excess in the setting of kidney insufficiency that were subsequently dose adjusted	During usual care, 23% of medications administered to adult inpatients with impaired kidney function were dosed in excess compared with 17% after alert implementation ($P<0.05$)
Historical cohort established for the fourth month period before alert implementation	Automated alert system built into the electronic medical record system that triggered when an order was made for a drug with a "threshold" creatinine clearance that was greater than the patient's most recently estimated creatinine clearance	Proportions of patients receiving at least one dose of a contraindicated medication	In the historical cohort, 87% of patients received at least one dose of a contraindicated drug versus 47% after alert implementation ($P<0.001$); in the alert group, 41% of instances in which an alert was given resulted in immediate cancellation of the order
Usual care	A computerized tool used to alert pharmacists at the time of dispensing to errors in drug selection and dosing in patients with kidney insufficiency	Proportion of mediation errors (target drugs that should be avoided or were inappropriately dosed)	The proportion of medication errors in the alert group (33%) was significantly lower than that for the control group (49%; $P<0.001$)
Usual care	A decision support system that provided dosing recommendations for targeted medication in adult patients with kidney insufficiency being discharged and displayed when the patient's estimated creatinine clearance was below	Proportion of targeted medications that were excessively dosed among all prescriptions for the targeted population of patients	Physicians in the control group had a larger occurrence of excessively dosing of medications (74% of prescriptions) compared with the control group (43%)
Prospective study with no control	Automated system to identify patients exposed to nephrotoxins in near real time and recommend more frequent creatinine measurement	Nephrotoxic medication exposure, AKI rates	After implementation, the rate of exposure to nephrotoxic medications decreased by 38%, and the rate of AKI decreased by 64%
Usual care before alert implementation (717 patients)	(*1*) A passive popup alert that displayed for patients with a 0.5-mg/dl increase in serum creatinine and prescribed a targeted medication; (2) an interruptive alert appearing when providers tried to exit from an ordering session without adjusting medication as suggested by the passive alert as required a provider action	Discontinuation or modification of a target medication within 24 h of alert; time to discontinuation or modification	In response to the interruptive alert, medication discontinuation/ modification improved from 35% preintervention to 53% postintervention ($P<0.001$); rates of this modification were significantly faster than those preintervention ($P<0.001$)
Usual care 6 mo before alert implementation	An automated system that calculated and updated kidney function and doses of key drugs adjusted for kidney function; academic detailing incorporated a 15-min session with clinicians on how to navigate the program	Rate of dosing conformity and management for key renally cleared drugs in hospitalized patients	Dosing conformity improved for enoxaparin (from 68% to 86%; $P=0.03$), gentamicin (from 63% to 87%; $P=0.01$), and vancomycin (from 47% to 77%; $P=0.07$); during episodes of acute kidney injury, medications excreted by the kidneys were held in 62% of cases in patients during the intervention period versus 38% of cases in patients in the preintervention period

for a pneumonia infection (9). Alerts may exacerbate this issue if providers place too much credence on the alert system rather than their own medical judgement. Careful consideration of a variety of factors, including patient risk factors and history, degree and type of injury, and their specific effects on volumes of distribution and other pharmacokinetic factors, and available alternative therapeutic strategies must be performed in the decision to continue such therapies during the course of kidney injury or resume them during the recovery. Because the speed and extent of recovery vary at the patient level, there is no hard boundary for nephrotoxin avoidance, and dosing becomes even more challenging. An individualized approach that includes a dynamic medication monitoring plan and frequent assessment throughout the entirety of disease progression is recommended and may be too complex to be captured for each patient by an overly broad and generalized alert (7).

Alert Intrusiveness

Alerting is a double-edged sword. There is a clear relationship between alert intrusiveness and efficacy, which we display in Figure 2. At the most extreme, "hard stop" alerts are highly effective but dramatically reduce provider autonomy and may introduce unintended consequences (such as when a truly necessary drug goes unused) as discussed above (33). At the other extreme, passive alerts delivered outside of the context of the electronic health record (EHR) may go ignored or unnoticed, such as was the case with our randomized trial of general alerts for AKI (34). The outlier on the intrusiveness-effectiveness line is "reflex" actions—scenarios where no alert is given but a clinical action is taken automatically. Commonly used for laboratory testing (where for example, a reflex differential may be applied to any white blood cell count over a given threshold), automated drug cessation or drug dosage adjustment in the face of changing kidney function has not been rigorously evaluated.

Limitations of Electronic Systems

Technical limitations can seriously limit the efficacy of alert systems, and they may explain why even "successful" alerts do not result in marked changes in provider behavior or patient outcomes. Integration of alerts at the point of care is likely to have a larger effect than "offline" alerting. This can be accomplished by trained personnel who personally interact with health care providers, although this approach is costly and time intensive. Direct integration within the EHR may be preferable, but many EHR systems are proprietary; a great deal of expertise is needed to create alerts within that environment.

The requirement that creatinine be in steady state to estimate a GFR is rarely met in hospitalized patients. To that end, eGFR or even absolute creatinine "thresholds" for drug dosing may overestimate dosages while kidney function is declining, and underestimate dosages when kidney function recovers. Several equations exist to estimate GFR in the setting of dynamic creatinine changes, but the use of these techniques to guide drug dosing has not been evaluated (35).

"False positive" alerts, in which a provider receives an alert that is incorrect or inappropriate, can severely hamper enthusiasm for the alert in general. For a nephrotoxic AKI alert, there are multiple potential points of failure. First, AKI itself may be misidentified on the basis of random variation in creatinine, changes in laboratory equipment standardization, or inclusion of individuals receiving dialysis (36). Second, nephrotoxic exposure may be misclassified by the alert if it unintentionally includes drugs that are not truly nephrotoxic, if it captures exposure to a drug that has already been discontinued, or if it fails to capture a drug due to a change in database coding for the agent (such as when a new manufacturer provides the agent to a hospital). Furthermore, alerts with specific dosing recommendations add another layer of complexity, which can lead to uninformative or incorrect alerts.

Finally, electronic alert systems may not be readily generalizable to different care settings, even in the relatively narrow space of inpatient nephrotoxic AKI alerts. Local practices with regards to drug dosing, pharmacist monitoring, and patient mix may have strong influence on alert effectiveness. This suggests that some "tailoring" of alert systems might be beneficial.

Figure 3 summarizes the key benefits, harms, and limitations of electronic alert systems discussed throughout the text.

Drug Alerts for Hospitalized Patients with CKD

Because of the more static nature of CKD, most studies evaluating the efficacy of drug dosage alerts have occurred in this setting.

An early study evaluating computerized clinical decision support for drug dosing in CKD analyzed 7490 hospitalized patients at a single tertiary care hospital (12). Before its introduction, 46% of prescriptions for kidney-cleared or nephrotoxic agents written had an inappropriate dose, and 65% had an inappropriate frequency. After its introduction, only 33% were deemed to have an inappropriate dose, and 41% had an inappropriate frequency ($P<0.001$ for both comparisons). Although this study shows that electronic clinical decision support can move the needle in terms of appropriate drug dosing, the high percentage of inappropriate doses even after its implementation suggests that it is far from a panacea.

In 2005, a group from Mt. Sinai reported on the development of a customized alert system that would detect inappropriate dosing of kidney-cleared medications (37). The system generated alerts each morning on the basis of the previous day's medication and kidney function data. Before implementation, 23% of medications administered were dosed "in excess" compared with 17% under the alert system. This system was notable for the fact that it was augmented *via* human interaction; trained pharmacists would contact care teams directly with dosing advice.

A small single-center study of 233 patients showed that "contraindicated" alerts can be highly efficacious for the discontinuation of potentially harmful agents (38). For each formulary drug, a "threshold" creatinine clearance was defined, below which an alert would fire to indicate that the drug was contraindicated. Before implementation, 89% of patients with an order for a contraindicated drug would receive at least one dose. After implementation, the rate of receipt of the contraindicated agents decreased to 47%,

almost entirely due to immediate cancellation of the order in the face of the alert. This study, like many clinical decision support studies, did not evaluate the clinical effect of these discontinuations.

Drug Alerts in Patients at Risk of AKI

It is common practice to avoid nephrotoxic agents in patients at particularly high risk of AKI, but few studies have systematically examined whether operationalizing and explicit support of that practice would improve patient outcomes.

Goldstein *et al.* (39) showed that an enhanced surveillance system targeting nephrotoxic agents could both modify a provider's behavior and reduce rates of AKI. At a large tertiary children's hospital, his team identified, in near real time, patients receiving an aminoglycoside or a combination of three other nephrotoxic medications. Patients identified in this manner ($n=1749$) were targeted for more frequent creatinine measurement (because hospitalized children often do not undergo daily laboratory monitoring). In this study, the rate of nephrotoxic medication exposure decreased by 38%, and the rate of AKI decreased by 64%, providing strong support for the hypothesis that reducing nephrotoxin exposure can reduce AKI rates.

In adult populations, theissue of increased creatinine screening is moot given a near-universal practice in the United States of at least daily measurement. Whether risk-based targeting of nephrotoxic agents before AKI would be an effective strategy to reduce AKI incidence is an intriguing one that has yet to be rigorously evaluated. Under such a framework, at-risk individuals (due to comorbidities or laboratory variables associated with future AKI) could be identified and targeted with efforts to reduce their nephrotoxin exposure (40).

Drug Alerts in the Setting of AKI

With its dynamic changes in drug pharmacokinetics, AKI presents both the most challenging and the most promising use case for drug-targeted alerts. A study that examined the effect of alert intrusiveness is particularly instructive in this case. In a quality improvement initiative, McCoy *et al.* (41) analyzed 1598 adult patients with AKI as defined by a 0.5-mg/dl increase in creatinine over 48 hours who had received one of 122 nephrotoxic or kidney-cleared medications. A passive alert within the medical record, indicating a rising creatinine and instructing the provider to discontinue or change the dose of key medications, had no effect on provider behavior. However, a more intrusive alert, requiring the provider to change the dose of or discontinue the agent or confirm that "this is the correct dose," led to a substantial increase in dose modification (from 35% to 53%; $P<0.001$). Again, it remains unclear whether these changes lead to beneficial clinical effect, but the study clearly shows that alert "intrusiveness" is a variable that needs to be strongly considered in alert design.

Although alerts and clinical decision support may be most effective when integrated into the daily workflow, a pre-/poststudy of 1001 patients in a geriatric teaching hospital showed that a clinical decision support system independent of the EHR could dramatically improve dosing of key kidney-cleared medications, including enoxaparin, gentamicin, and vancomycin, when accompanied by comprehensive academic detailing (42). Notably, during episodes of acute kidney impairment, these drugs were held in 38% of patients preintervention and 62% of patients postintervention ($P=0.01$). Longer-term clinical outcomes were not assessed.

Table 1 provides a summary of the relevant literature, highlighting the use of electronic nephrotoxin alert systems in the setting of both CKD and AKI.

Methods of Evaluation

Given the risk of alert fatigue, all alerts should be evaluated to ensure effectiveness. The minimum bar for effectiveness is a practical measure—the rate of nephrotoxic medication discontinuation, for example, or the rate of appropriate dosing for kidney-cleared medications. Although this standard may be sufficient to show that the alert is acting as intended, it does not capture the off-target effects of alerts as described above, and thus, a more stringent metric for alert efficacy should be evaluated. Hard clinical outcomes, like the rate of dialysis or death, may be impractical to assess due to the low prevalence of these events and the likelihood of secular trends in patient characteristics influencing the results (in the absence of a randomized trial). However, AKI metrics, including peak achieved creatinine and duration of AKI, may offer reasonable surrogates for these outcomes (45).

Beyond simply reassuring the designers of alert systems that their work has been put to good use, evidence of clinical effectiveness may increase the faith that health care providers put in the alert system, leading to broader adoption (46). As such, feedback to those receiving alerts regarding performance over time may be particularly important, because multiple studies have shown that alert efficacy may wane as the novelty wears off. In terms of measuring alert effectiveness, change in drug dosing or cessation of the nephrotoxic agent is a critical practical measure. However, more broadly, the clinical efficacy of a drug-targeted AKI alert should be assessed in terms of its ability to show improved clinical outcomes, such as a reduced rate of AKI progression, dialysis, or (perhaps) death.

Summary and Conclusions

Electronic alerts for AKI in the setting of nephrotoxin exposure hold promise to dramatically change the rates of nephrotoxin exposure and modestly improve clinical outcomes in patients with AKI. However, the potential benefits of these alerts need to be weighed against the very real concern of increasing alert fatigue and the need to ensure that systems are robust with an extremely low false positive rate. As shown in the examples above, the intrusiveness, timing, and mode of alerting as well as the type of information relayed must all be considered and optimally balanced to create the most beneficial alert while mitigating associated risks. Randomized trials generating long-term data of outcomes in hospitalized patients with nephrotoxin exposure are warranted to better understand

the utility and risks associated with the adoption of electronic alerting.

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Disclosures

None.

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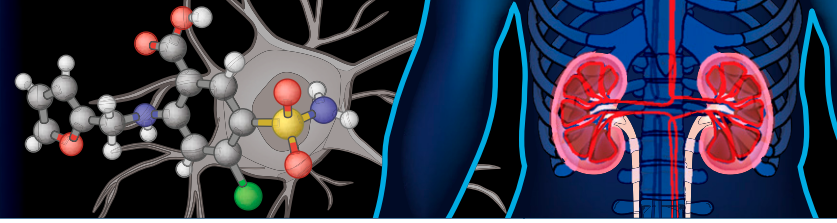

Clinical Pharmacology of Oral Anticoagulants in Patients with Kidney Disease

Nishank Jain[1,2] *and Robert F. Reilly*[3,4]

Abstract

Oral anticoagulants are commonly used drugs in patients with CKD and patients with ESKD to treat atrial fibrillation to reduce stroke and systemic embolism. Some of these drugs are used to treat or prevent deep venous thrombosis and pulmonary embolism in patients with CKD who undergo knee and hip replacement surgeries. Warfarin is the only anticoagulant that is approved for use by the Food and Drug Administration in individuals with mechanical heart valves. Each oral anticoagulant affects the coagulation profile in the laboratory uniquely. Warfarin and apixaban are the only anticoagulants that are Food and Drug Administration approved for use in patients with CKD and patients with ESKD. However, other oral anticoagulants are commonly used off label in this patient population. Given the acquired risk of bleeding from uremia, these drugs are known to cause increased bleeding events, hospitalization, and overall morbidity. Each anticoagulant has unique pharmacologic properties of which nephrologists need to be aware to optimally manage patients. In addition, nephrologists are increasingly asked to aid in the management of adverse bleeding events related to oral anticoagulant use in patients with CKD and patients with ESKD. This article summarizes the clinical pharmacology of these drugs and identifies knowledge gaps in the literature related to their use.

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Introduction

The number of patients with CKD and patients with ESKD is increasing in the United States on the basis of the National Health and Nutrition Examination Survey data from 1999 to 2014 (1). Although heart failure, thrombotic cardiovascular events, and sudden cardiac death are common in CKD and ESKD, this population is also at a disproportionately higher risk of nonvalvular atrial fibrillation (AF) compared with the general population. Prevalence of AF increases as kidney disease worsens, and it is close to 15% by the time that patients with CKD become dialysis dependent, which is more than three times that of age-matched controls (2). Use of oral anticoagulants is common, and these agents are among the top 15 drugs prescribed to patients with CKD and patients with ESKD enrolled in Medicare Part D, Medicare Advantage, or Managed Care prescription drug programs (1). Warfarin is one of the most commonly prescribed oral anticoagulants. In the general population, newer oral anticoagulants (dabigatran, rivaroxaban, apixaban, and edoxaban) reduce risk of stroke or systemic embolism and bleeding versus warfarin in patients with AF, and they are increasingly prescribed in patients with CKD and patients with ESKD. Newer anticoagulants may be favored over warfarin in patients with ESKD and calciphylaxis (3). The reader can refer to previous review articles that have discussed extensively the clinical utility of oral anticoagulants in CKD (4). This review article will focus on the pharmacology of commonly used oral anticoagulants that are important in nephrology practice. In addition, it will identify knowledge gaps regarding use of these drugs in this patient population.

Warfarin

Pharmacology

Warfarin is the oral anticoagulant with which clinicians have the most experience. It is a racemic mixture of two optically active isomers (R and S) in equal proportion (5). Its pharmacokinetic and pharmacodynamic (PK/PD) properties are shown in Tables 1 and 2. Common drug-drug interactions are shown in Table 3. Polymorphisms in vitamin K epoxide reductase gene and cytochrome P450 type 2C9 (CYP2C9) are not race specific, and they account for 25% and 10%, respectively, of the interindividual variability in warfarin dosing (6). Vitamin K epoxide reductase genotype may be the best predictor of warfarin dose, because it is responsible for the conversion of vitamin K epoxide to vitamin K (Figure 1) (6). CYP2C9 alleles (*e.g.*, CYP2C9*2 and *3) are poor metabolizers, leading to prolonged $t_{1/2}$ compared with the wild type (*1 allele) (5). The observed frequencies of CYP2C9*2 are 8%–19% in whites and <4% in blacks. The corresponding frequencies for *3 alleles are 6%–10% and <2%, respectively. The mechanism of action of warfarin is shown in Figures 1 and 2.

Laboratory Measurement of Anticoagulant Effect

Internal normalized ratio (INR) is the most common test used to monitor warfarin response. Drugs, dietary

Table 1. Summary of pharmacokinetic and pharmacodynamic properties of commonly used oral anticoagulants

OAC	Type	Prodrug	Pharmacokinetics			Pharmacodynamics: Binding to Effector
			Metabolism	Renal Dose Adjustment	Dialyzable	
Warfarin	Vitamin K–dependent factor inhibitor	No	Extensive metabolism by CYP2C9	No	No	Irreversible
Dabigatran	Direct thrombin inhibitor	Yes	Metabolized by esterases, 80% excreted by kidney	Yes	Yes	Reversible
Apixaban	Free and clot-bound Xa inhibitor	No	Metabolized in liver by CYP3A4, then excreted in feces and kidney (25%), no active metabolite	No	Small	Reversible
Rivaroxaban	Free and clot-bound Xa inhibitor	No	66% Excreted by kidney, 36% unchanged, minimal in feces	Yes	No	Reversible
Edoxaban	Free Xa inhibitor	No	50% Excreted unchanged by the kidney, 10% hydrolyzed by carboxyesterase 1	Yes	No	Reversible

OAC, oral anticoagulant; CYP2C9, cytochrome P450 type 2C9; Xa, factor Xa; CYP3A4, cytochrome P450 type 3A4.

changes, and disease processes alter warfarin effects. Therefore, its use requires frequent monitoring to maximize individual time spent in the therapeutic range on the basis of an INR between 2.0 and 3.0. Compared with individuals spending the least amount of individual time in the therapeutic range (<57%), those with the highest amount of individual time spent in the therapeutic range (>73%) experienced lower rates of stroke or systemic embolism (2% versus 1%), major bleeding (5% versus 3%), and all-cause mortality (7% versus 3%).

Pharmacology in Kidney Disease

The PK/PD of warfarin in CKD and ESKD is not well established (7). Clinical practice guidelines do not recommend dosage reduction for CKD or ESKD (5,8). Limdi *et al.* (9,10) found that mean (95% confidence interval [95% CI]) dose reductions of 10% (95% CI, 4% to 14%) and 19% (95% CI, 11% to 26%) were required in patients with eGFR=30–59 and <30 ml/min per 1.73 m^2 compared with individuals with eGFR≥60 ml/min per 1.73 m^2 to maintain therapeutic warfarin dosing. This cross-sectional analysis also adjusted for other confounders in the multivariable statistical model, and thus, interpretation of dose reductions solely on the basis of eGFR may be an oversimplified approach. Yet, it provides major evidence of increased exposure of drugs cleared by the liver in patients with CKD. With a single warfarin dose (0.75 mg/kg), individuals with GFR of 30–59 ml/min per 1.73 m^2 had a shorter $t_{1/2}$ at 29.9±5.0 versus 44.8±6.0 hours in healthy controls. An increase in warfarin clearance was observed from 2.6 ml/kg per hour in healthy controls to 3.7 ml/kg per hour in CKD (7). It remains to be established whether the dialysis procedure (hemodialysis or peritoneal dialysis) results in changes in warfarin kinetics and dynamics. Warfarin has significant drug-drug interactions that are especially important given the polypharmacy that is so prevalent in patients with CKD and patients with ESKD (Table 3).

Reversal of Antithrombotic Effects

Warfarin's antithrombotic effects are reversed by low doses of vitamin K (Table 4). When pharmacologic doses

Table 2. Additional pharmacokinetic properties in those with normal kidney function

OAC	Cmax, h	$t_{1/2}$, h	Protein binding, %	V_D, L	Bioavailability, %
Warfarin	2–6	42	97–99	10	99
Dabigatran	1–2	12–14	38	50–70	3–7
Apixaban	3–4	12	87	21	50
Rivaroxaban	2–4	6–13	>90	50	66–100
Edoxaban	1–2	10–14	55	107	62

OAC, oral anticoagulant; Cmax, peak concentration; V_D, volume of distribution.

Table 3. Common drug-drug interactions of oral anticoagulants

Drug	Increase Anticoagulant Effects	Decrease Anticoagulant Effects
Warfarin	Amiodarone, fluconazole, tigecycline, voriconazole, fluoroquinolones, verapamil, diltiazem, other anticoagulants, antiplatelet drugs, NSAIDs, and SSRIs	Rifampin, phenobarbital, carbamazepine, cigarette smoking
Dabigatran	Amiodarone, verapamil, ketoconazole, dronaderone, clopidogrel, enoxaparin, other anticoagulants, antiplatelet drugs	Rifampin
Apixaban	Ketoconazole, other anticoagulants, antiplatelet drugs	Rifampin
Rivaroxaban	Other anticoagulants, antiplatelet drugs, fluconazole, ketoconazole, erythromycin, and clarithromycin	Rifampin, phenytoin, carbamazepine, St. John's Wort
Edoxaban	Other anticoagulants, antiplatelet drugs,	Rifampin

NSAID, nonsteroidal anti-inflammatory drug; SSRI, serotonin reuptake inhibitor.

of vitamin K (phytonadione 2.5–5 mg) are administered, reduced vitamin K is generated by a mechanism that bypasses epoxide reductase (*via* vitamin K reductase) that is less sensitive to warfarin (Figure 1) (5). Large vitamin K doses (10 mg) can result in warfarin resistance for >1 week (5). The American College of Chest Physicians guidelines recommend, for INRs≥9 and no bleed, a single oral 2.5- to 5-mg dose to bring the INR down in 1–2 days (5). For serious bleeding, regardless of INR value, 10 mg is administered parentally, and it is supplemented by fresh frozen plasma, prothrombin complex concentrate, or recombinant factor VIIa. These measures are repeated every 12 hours if the INR remains elevated (5). Because hemorrhagic effects can be prolonged in patients with CKD and patients with ESKD for a given INR value compared with in non-CKD individuals (11), clinicians should consider repeated therapy to ensure adequate reversal.

Efficacy and Safety

Compared with those with normal kidney function, CKD, especially GFR<30 ml/min per 1.73 m^2, or ESKD complicates warfarin therapy. Specifically, lower doses are required to maintain therapeutic INR. Greater fluctuations in INR values with lower individual time in the therapeutic range and higher risks of major bleeding events for any given INR value are reported (9,10). In an observational study of 1273 long-term warfarin users, one third had a GFR of <60 ml/min per 1.73 m^2 (11). Compared with individuals with GFR of >60 ml/min per 1.73 m^2, those with GFR of 30–44 ml/min per 1.73 m^2 and those with GFR<30 ml/min per 1.73 m^2 had 2.2- and 5.8-fold higher risks, respectively, of major bleeding events at an INR value ≥4. GFR did not modify risk of hemorrhage for INR values <4 (11).

Because higher stroke rates were reported in patients with ESKD with versus without AF (4.57 versus 0.48 per 100 person-years, respectively) (12), previous cost utility

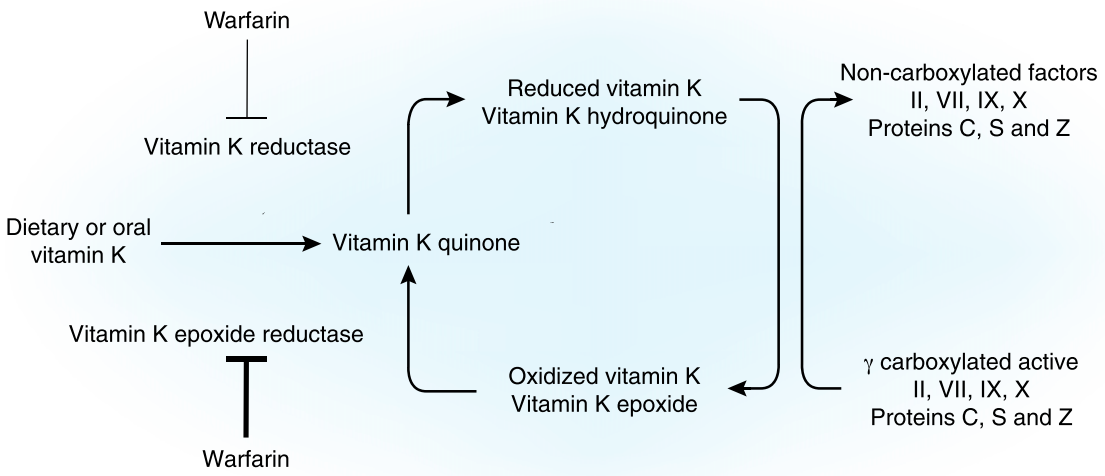

Figure 1. | Carboxylation of vitamin K–dependent proteins requires the reduced form of vitamin K, γ-glutamyl carboxylase enzyme, molecular oxygen, and carbon dioxide. Because body stores of vitamin K are low, the oxidized (inactive) form of vitamin K is recycled to the reduced (active) form by vitamin K epoxide reductase, which is inhibited by warfarin. Inhibition results in reduced hepatic synthesis of these clotting factors and reduction in their activities by 40%–50%.

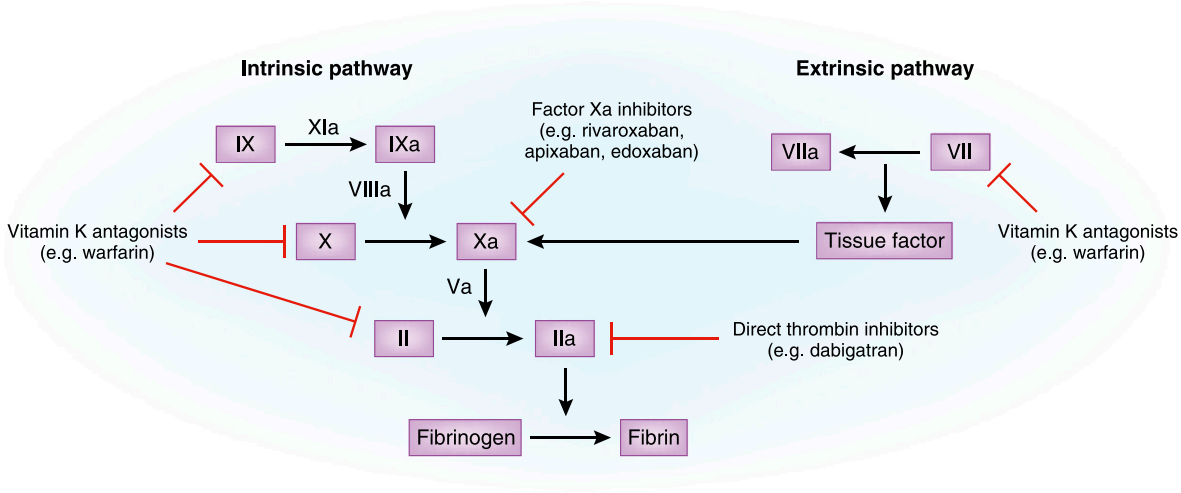

Figure 2. | **Oral anticoagulants act at different sites in the coagulation cascade for their anticoagulant effects.**

analyses reported an increase in quality-adjusted life years with aspirin or warfarin treatment (13). However, warfarin increases bleeding risk, including intracranial hemorrhage, in patients with ESKD. In a retrospective study of patients with ESKD and AF, warfarin doubled stroke risk, presumably hemorrhagic, compared with no treatment (14). Another study evaluated patients with ESKD in the Fresenius Medical Care North America (FMCNA) database and reported 27% higher death risk with warfarin treatment (15). Observational studies are fraught with selection bias, especially because patients with ESKD and AF may be more likely to die compared with individuals with ESKD without AF. Data are limited to confirm or refute these concerns. There is concern of increased vascular calcification and calciphylaxis with warfarin given that it reduces function of vitamin K–dependent vascular calcification inhibitors, such as matrix Gla proteins (14,16). Finally, there are concerns about the possibility of AKI secondary to glomerular hemorrhage due to thrombin depletion in patients on warfarin with INR>3 in whom there is no other identifiable etiology of AKI (17). It is also believed to result in accelerated progression of CKD and worsen all-cause mortality in the short and long term (17). However, exact mechanisms and clinical presentation remain elusive to date.

Despite a Food and Drug Administration (FDA) black box warning for warfarin use in patients with kidney dysfunction due to increased risk of major bleeding, it is still commonly used. Furthermore, clinical practice guidelines continue to recommend warfarin in treating AF among patients with CKD and patients with ESKD (18). The American Heart Association 2014 updated guidelines for anticoagulation management in AF recommend warfarin as the drug of choice in patients with advanced CKD (creatinine clearance <30 ml/min) and patients with ESKD (8,19). The jury is still out regarding potential benefits and risks. If this high-risk patient population is not treated, it is estimated that stroke rate, including intracranial hemorrhage, would be approximately 7% (18). However, three distinct observational studies reported that warfarin did not reduce ischemic strokes among patients with ESKD. In addition, these studies reported an alarmingly higher intracranial hemorrhage rate compared with in the general population (3% versus 1% per year, respectively) (18).

Direct Thrombin Inhibitor—Dabigatran

Pharmacology

Dabigatran etexilate, 150 mg twice daily, is FDA approved to prevent stroke or systemic embolism in patients with AF. Nonspecific, ubiquitous esterases rapidly convert this nonpeptide prodrug into a potent, direct, and selective inhibitor of free and fibrin-bound thrombin (Table 1) (20).

Table 4. Reversal agents for oral anticoagulants and hemodialysis as an option to reverse antithrombotic effects

Reversal modality	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Reversal by antidotes					
Prothrombin complex concentrate	Yes	No	Yes	Yes	Yes
Recombinant factor VIIa	Yes	No	Yes	Yes	Yes
Fresh frozen plasma	Yes	No	Yes	Yes	Yes
Factor VIII inhibitor bypass activity	Not reported	Yes	Yes	Yes	Yes
Specific antidote	No	Idaracizumab		Investigational (andexanet alfa)	
Dialysis as a treatment option for major bleeding events					
Hemodialysis	No	Yes	No	No	No

Table 5. Comparative efficacy and safety data on dabigatran versus warfarin in patients with kidney disease and atrial fibrillation (36–41)

	Study Population	Sample Size of CKD Subgroup	Findings	Adjusted Risk Ratio (95% Confidence Interval)
Dabigatran in patients with CKD				
Lauffenburger *et al.* (37)	Patients having commercial or Medicare supplemental insurance	6727	Reduced risk of S/SE	0.74 (0.57 to 0.96)[a]
			Increased risk of the composite of major GI bleeding, hemorrhagic stroke, ICH, or other bleeding	1.52 (1.27 to 1.81)[a]
Hernandez *et al.* (38)	5% Random sample of Medicare beneficiaries	2964	Increased risk of any bleeding	1.11 (1.02 to 1.21)[a]
			Increased risk of major bleeding	1.55 (1.32 to 1.82)[a]
Majeed *et al.* (39)	Pooled analyses of five phase 3 RCTs	1034 with any bleeding event, no mention of percentage with CKD	30-d Mortality after the first bleeding event was lower for all of those who experienced any bleeding event in the five RCTs (no separate CKD subgroup analysis reported)	0.66 (0.44 to 1.00)[b]
Graham *et al.* (40)	Medicare beneficiaries	13% of 134,414 had CKD	No CKD subgroup analysis, results reported for the overall cohort	
			Reduced risk of ischemic stroke	0.80 (0.67 to 0.96)[a]
			Reduced risk of ICH	0.34 (0.26 to 0.46)[a]
			Increased risk of major GI bleeding	1.28 (1.14 to 1.44)[a]
			Reduced risk of all-cause mortality	0.86 (0.77 to 0.96)[a]
Romanelli *et al.* (36)	Meta-analysis	348,750 Patients and no CKD subgroup analysis	No CKD subgroup analysis, results reported for the overall cohort	
			Reduced risk of S/SE	0.92 (0.84 to 1.01)[a]
			Reduced risk of ICH	0.44 (0.34 to 0.59)[a]
			Increased risk of major GI bleeding	1.23 (1.01 to 1.50)[a]
Dabigatran in patients on hemodialysis				
Chan *et al.* (41)	Fresenius Medical Care of North American database of patients on hemodialysis	8345	Increased risk of hospitalization or death from bleeding	1.48 (1.21 to 1.81)[c]
			Increased risk of hemorrhagic death	1.78 (1.18 to 2.68)[c]

S/SE, stroke or systemic embolism; GI, gastrointestinal; ICH, intracranial hemorrhage; RCT, randomized, controlled trial.
[a]Adjusted hazard ratio.
[b]Adjusted odds ratio.
[c]Adjusted rate ratio.

PK/PD properties are shown in Tables 1 and 2. Common drug-drug interactions are shown in Table 3. Its capsule (75 or 150 mg) contains dabigatran-coated pellets with a tartaric acid core to augment bioavailability at low pH. The core increases dyspepsia risk and gastrointestinal bleeding, especially with the 150-mg dose (20). Patients should not chew, break, or open capsules, because bioavailability increases dramatically (21). Substantial interindividual drug exposure variability exists (22). Dabigatran is approved at lower doses (75 mg twice daily), with a creatinine clearance of 15–30 ml/min (21).

Laboratory Measurement of Anticoagulant Effect

Activated partial thromboplastin time (APTT) is better than prothrombin time (PT) to detect dabigatran presence, but it cannot reliably distinguish between therapeutic and subtherapeutic concentrations (Table 4) (20,23). A normal thrombin time has the best negative predictive value to exclude the presence of dabigatran (20,23). Ecarin, a metalloproteinase, cleaves prothrombin to meizothrombin. Dabigatran inhibits this step. Ecarin-based assays, such as the ecarin clotting time, are highly sensitive and correlate strongly with drug concentrations. Studies showed that thrombin time and ecarin clotting time are linearly correlated with drug concentration measured by liquid chromatography tandem mass spectrometry (23).

Pharmacology in Kidney Disease

An open label, controlled study investigated PK/PD properties of a single 150-mg dabigatran dose in 23 patients with CKD and 50 mg in six patients with ESKD. The comparator group (six non-CKD controls) received two doses of 150 mg (standard dose) (24). Versus controls, areas under the plasma concentration-time curve (AUCs) were 1.5-, 3.2-, and 6.3-fold higher in patients with CKD and creatinine clearances of 50–80, 30–50, and ≤30 ml/min, respectively. Time to maximal plasma concentration (Cmax) was similar in patients with CKD and controls.

Elimination $t_{1/2}$ doubled in patients with CKD (creatinine clearance ≤30 ml/min) compared with non-CKD controls. Although six patients with ESKD received a reduced dose (50 mg), AUC was twofold higher than in non-CKD controls. A single hemodialysis session removed 62%–68% of the 50-mg dose. APTT and ecarin clotting time increased in correlation with changes in plasma drug concentration. Another PK/PD study was conducted in 15 patients with creatinine clearance of 15–30 ml/min. Participants received 75 mg twice daily, a dose resulting in mean steady-state drug exposure without drug accumulation (25). These studies suggest that drug exposure correlates with kidney disease severity and prescribed dose, which can be measured by APTT or ecarin clotting time.

Reversal of Antithrombotic Effects

There are patient reports using fresh frozen plasma and prothrombin complex concentrate to reverse dabigitran's effects in patients with major bleeding (26). A recent randomized, controlled trial (RCT) in subjects with normal kidney function raised questions about the efficacy of prothrombin complex concentrate as an effective reversal agent (27). In another study in subjects with normal kidney function, nonspecific anti-inhibitor coagulant complex (*e.g.*, factor VIII inhibitor bypass activity) but not recombinant factor VIIa reversed dabigatran's anticoagulant effects (28). No studies have evaluated these agents in patients with CKD and patients with ESKD. A patient series of 11 life-threatening dabigatran-related major bleeding episodes reported use of hemodialysis and continuous venovenous hemofiltration (29). A PK/PD study of dabigatran 150 mg twice daily for 3 days in seven patients on hemodialysis reported 49% and 59% drug removal with blood flow rates of 200 and 400 ml/min, respectively, over a 4-hour treatment (30). Another study reported 62%–68% dabigatran removal with a single dialysis session (24). Although studies are limited by lack of control groups, randomization, and small sample size, available data suggest a possible role for kidney replacement therapy in reversal of dabigatran's antithrombotic effects.

Recently, the FDA approved idarucizumab to reverse the antithrombotic effects of dabigatran (31). As a humanized mAb fragment directed against dabigatran and its acyl-glucuronide metabolites, its binding affinity to dabigatran is higher than dabigatran to thrombin, thus neutralizing the anticoagulant effect immediately after a single 5-g intravenous dose (32). Nearly one third (32%) of idarucizumab is excreted in urine, and the remainder undergoes metabolism primarily in kidney (32). In 12 subjects with creatinine clearance ≥60 to <90 ml/min and six subjects with creatinine clearance ≥30 to <60 ml/min, total antidote clearance was reduced, resulting in higher drug exposure by 44% and 84%, respectively (32). The package insert recommends no dose reduction for kidney dysfunction. More studies are needed to assess its efficacy in patients with CKD and patients with ESKD.

Efficacy and Safety

After FDA approval, patient reports of major bleeding were reported in frail elderly individuals, patients with CKD, and patients with ESKD (26,33). In the Randomized Evaluation of Long-Term Therapy Trial, 19% of patients had a baseline creatinine clearance <50 ml/min, and individuals with baseline creatinine clearance <30 ml/min were excluded (34). A subgroup analysis reported lower rates of stroke or systemic embolism with dabigatran 150 mg twice daily versus warfarin across all creatinine clearance categories (≥80, 50 to <80, and <50 ml/min) (35). Lower major bleeding rates were observed only in participants with creatinine clearance ≥80 ml/min. Table 5 summarizes four retrospective cohort studies and one meta-analysis reporting comparative effectiveness and safety data for dabigatran versus warfarin in CKD subgroups, and they concluded that dabigatran versus warfarin reduces risk of stroke or systemic embolism and intracranial hemorrhage, with an increased risk of gastrointestinal bleeding events (36–40). There is only one study in patients on hemodialysis using the FMCNA database; it reported a 1.5-fold higher risk of death or hospitalization from bleeding with dabigatran versus warfarin (Table 5) (41).

Factor Xa Inhibitors

Rivaroxaban

Rivaroxaban is FDA approved in patients with AF to prevent stroke or systemic embolism (42). It is also FDA approved for deep venous thrombosis (DVT) and pulmonary embolism (PE) prophylaxis after knee and hip replacement (42,43). Like dabigatran, it is not approved in patients with mechanical heart valves. Oral bioavailability varies with dosing strength: 80%–100% with a 10-mg dose and 66% with a 20-mg dose. Other PK/PD properties are shown in Tables 1 and 2 (20). It is prescribed at a fixed oral dose with the evening meal: 20 mg/d for patients with a creatinine clearance of >50 ml/min and 15 mg/d for patients with a creatinine clearance of 30–50 ml/min (42). It should be avoided in patients with AF and a creatinine clearance of <15 ml/min (42). With a creatinine clearance of 15 to 50 ml/min the package insert recommends a reduced dose of 15 mg once daily with the evening meal in patients with nonvalvular atrial fibrillation. Rivaroxaban is not recommended for other indications with a creatinine clearance <30 ml/min. It does not interact with foods and interacts minimally with other drugs (Table 3). For DVT and PE prophylaxis, dosage is 10 mg/d. Rivaroxaban has a shorter $t_{1/2}$ and more rapid onset of action than warfarin (43). Timing of initiation after procedures and daily adherence are prerequisites for clinical success (43). It is typically started 6–10 hours after surgery for DVT/PE prophylaxis, and it is continued for 35 days after hip replacement and 12 days after knee replacement (42). To transition from heparin to rivaroxaban, infusion is stopped, and rivaroxaban is started simultaneously. When transitioning from low molecular weight heparin, rivaroxaban is initiated within 2 hours of the next scheduled administration (42).

Pharmacology in Kidney Disease

A subgroup analysis of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) with impaired creatinine clearance (<80 ml/min) reported no effect of kidney

disease on rivaroxaban's effectiveness and safety (44). A PK/PD study extended this finding by reporting similar AUCs (plasma concentration-time curve) in patients with ESKD and a 10-mg dose and healthy controls with a 20-mg dose (45). However, other controlled PK/PD studies challenged these findings and reported a 56% increase in AUC in patients with ESKD after a 15-mg dose administered postdialysis (46). Predialysis administration resulted in reduced drug exposure by only 5%. Finally, a PK/PD study of a single 10-mg dose was conducted in 24 patients with CKD (creatinine clearance <80 ml/min) and eight healthy controls (creatinine clearance ≥80 ml/min) (47). Compared with controls, the AUCs were 1.4-, 1.5-, and 1.6-fold higher with creatinine clearances of 50–80, 30–50, and <30 ml/min, respectively. The AUCs (factor Xa inhibition-time curve) were 1.5-, 1.9-, and 2.0-fold, respectively. This study suggests that reduced rivaroxaban clearance with worsening creatinine clearance resulted in increased drug exposure (47). Rivaroxaban is likely to accumulate in patients with CKD and patients with ESKD even at lower doses (10 or 15 mg/d), and it is poorly cleared by hemodialysis.

Apixaban

Apixaban is FDA approved for reduction of stroke or systemic embolism in patients with AF at 5 mg twice daily (48). With serum creatinine ≥1.5 mg/dl, age ≥80 years old, or body weight ≤60 kg, a reduced dose of 2.5 mg twice daily is recommended (48). It is also approved for DVT/PE prophylaxis after hip and knee replacement at 2.5 mg twice daily (48) and treatment of DVT/PE at 10 mg twice daily for a week followed by 5 mg twice daily (48). It is not approved for use with mechanical heart valves (48). PK/PD properties are shown in Tables 1 and 2. Drug-drug interactions are minimal (Table 3) (43).

Pharmacology in Kidney Disease

No significant kinetic changes were observed in peak plasma drug concentration (Cmax) or AUC among patients with CKD (creatinine clearance of 15–29 ml/min) and patients with ESKD (48). An open label, parallel group, single 5-mg dose PK/PD study was conducted in eight patients with ESKD and eight healthy controls (49). After 2 hours of drug administration, a 4-hour hemodialysis session was performed with dialysate flow rate of 500 ml/min and blood flow rate of 350–500 ml/min. The AUC in patients with ESKD was 36% higher versus controls (49). Because of its high degree of protein binding, dialysis clearance is low (18 ml/min), resulting in a 14% decrease in drug exposure (49). In a recent retrospective analysis of patients on hemodialysis, cumulative days of apixaban use in an outpatient setting, higher total daily apixaban doses, and total hemodialysis sessions were independent risk factors for bleeding events (adjusted odds ratio, 13.07; 95% CI, 1.54 to 110.54; adjusted odds ratio, 1.72; 95% CI, 1.20 to 2.48; and adjusted odds ratio, 2.04; 95% CI, 1.06 to 3.92, respectively) (50). Another PK/PD study prescribed a single 10-mg dose to 24 patients with CKD and various categories of creatinine clearance and eight healthy controls (51). Compared with controls, geometric mean AUCs increased by 16%, 29%, and 38% in patients with CKD and creatinine clearances of 50–80, 30–50, and <30 ml/min, respectively. Overall, elimination $t_{1/2}$ was slightly increased in all subjects with CKD (17 hours) versus controls (15 hours). A direct linear relationship was observed between apixaban plasma concentration and antifactor Xa activity. These studies suggest that apixaban accumulates in patients with CKD and patients with ESKD and that it is poorly dialyzable. In another PD/PK study seven hemodialysis patients were given apixaban at 2.5 mg twice daily for eight days. The AUC, Cmax, and Cmin all increased when measured at day 8 compared to day 1 suggesting accumulation of the drug. At day 8 drug levels were still within the normal reference range. Drug levels comparing day 5 versus day 8 suggested that a steady state had been reached. Despite that it still would be of interest to examine levels with a longer duration of exposure (52).

Edoxaban

Edoxaban was FDA approved after a trial that established noninferiority compared with warfarin in patients with AF (53). It is also approved for treatment of DVT/PE only after an initial 5- to 10-day treatment with parenteral anticoagulation (19). It is recommended at 60 mg once daily for patients with creatinine clearance of 50–95 ml/min and 30 mg once daily for patients with creatinine clearance of 15–50 ml/min (54). PK/PD properties are shown in Tables 1 and 2. Common drug-drug interactions are shown in Table 3.

Pharmacology in Kidney Disease

Drug exposure increases by 32%, 74%, and 72% with creatinine clearances of 50–80, 30–50, and <30 ml/min, respectively (55). Although its molecular weight is 738 g/mol and it is only 55% protein bound, it is poorly cleared by dialysis (9% with a blood flow rate of 350 ml/min, a dialysate flow rate of 500 ml/min, and an F180NR dialyzer), possibly due to the large volume of distribution (107±20 L) (56).

Laboratory Measurement of Anticoagulant Effects

PT prolongation occurs to a greater degree than APTT prolongation with factor Xa inhibitors (Table 4) (20). A prolonged PT on warfarin does not equate to a similar anticoagulant effect on factor Xa inhibitors with the exact same PT value (23). Compared with PT and APTT assays, chromogenic anti-Xa activity assay (*e.g.*, Rotachrom) may be more reliable and accurate (20,23). There is strong correlation between antifactor Xa activity and factor Xa inhibitor concentration (r^2=0.95–1.00) (20). There are no FDA-approved kits that can be used for universal standardization of the anti-Xa activity assay.

Reversal of Antithrombotic Effects

Prothrombin concentrate complex, recombinant factor VIIa, and factor VIII inhibitor bypass activity can reverse their anticoagulant effects (Table 4) (27,28,57–60). There are no specific antidotes. Andexanet alfa, a modified recombinant human factor Xa molecule that acts as a decoy molecule, is under investigation (61).

Efficacy and Safety

The RCT (the ROCKET-AF) that led to FDA approval of rivaroxaban for AF included participants with CKD

and excluded individuals with a creatinine clearance <30 ml/min (62). On the basis of studies in the general population, newer oral anticoagulants (dabigatran, rivaroxaban, or apixaban) compared with warfarin were more effective in reducing stroke or systemic embolism without an increased risk of intracranial hemorrhage and gastrointestinal bleeding (63). As a result, off-label use is increasing in patients with a creatinine clearance of <30 ml/min and ESKD (41). A study of the FMCNA database of patients with AF on chronic hemodialysis reported a 1.7-fold higher risk of death or hospitalization from bleeding with rivaroxaban versus warfarin (adjusted rate ratio, 1.71; 95% CI, 0.94 to 3.12) (41).

With apixaban, there is one published patient report of a major bleeding event noted in a patient on hemodialysis (64). Apixaban was superior to warfarin in reducing stroke or systemic embolism rates and major bleeding among participants with kidney dysfunction in the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation Trial (65). A meta-analysis of RCTs comparing newer oral anticoagulants (dabigatran, rivaroxaban, and apixaban) with warfarin reported no difference in stroke, systemic embolism risk, or major bleeding in the CKD subgroup (relative risk, 0.64; 95% CI, 0.39 to 1.04 and relative risk, 0.89; 95% CI, 0.68 to 1.16, respectively) (66). Another meta-analysis reported reduced bleeding risk in the CKD subgroup (risk ratio, 0.80; 95% CI, 0.66 to 0.96) (67). In addition, bleeding rates were similar between individuals with creatinine clearance of 50–80 versus 30–50 ml/min on apixaban (67).

Compared with participants with creatinine clearance >50 ml/min, individuals with creatinine clearance of 30–50 ml/min in the Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation-Thrombolysis in Myocardial Infarction Study 48 reported similar stroke or systemic embolism risk on edoxaban (68). Another subgroup analysis reported similar findings and a 24% reduction in bleeding risk (adjusted hazard ratio, 0.76; 95% CI, 0.58 to 0.98) (19). Finally, no difference in bleeding was reported between 15- and 30- to 60-mg/d doses in patients with GFR 15–30 ml/min per 1.73 m^2 (19).

A recent Cochrane review reported reduced risk of stroke or systemic embolism and similar risk of major bleeding among patients with AF and CKD treated with factor Xa inhibitors versus warfarin (risk ratio, 0.81; 95% CI, 0.65 to 1.00 and risk ratio, 0.79; 95% CI, 0.59 to 1.04, respectively) (69). For both rivaroxaban and apixaban major clinical trials excluded patients on hemodialysis. With both drugs, at reduced dosages in hemodialysis patients, drug concentrations approximate those found in patients without kidney disease. However, the number of patients studied is very small and no conclusions can be drawn regarding their safety or efficacy, and caution should be exercised with their use in this patient population.

Gaps in the Literature

Although patients with CKD and patients with ESKD account for nearly 10% of the overall Medicare paid claims costs and although oral anticoagulant drugs are one of the top ten prescription drugs of Medicare prescription drug expenditure (70), comparative efficacy and safety data remain limited to support use of one oral anticoagulant over another in patients with CKD stages 4–5 or ESKD. Because these patients suffer from increased rates of hospitalization, adverse outcomes, and high health care–related costs (71), RCTs to investigate efficacy and safety of oral anticoagulants to improve hard clinical outcomes are critically important. Finally, there is lack of a standardized approach to assess kidney function in research, because debate continues regarding the preferred method for adjusting drug dosage. For example, the Modification of Diet in Renal Diseases eGFR calculation and the Cockcroft Gault creatinine clearance calculation were reported to over- or underestimate kidney function in various clinical settings (72,73).

Summary

Oral anticoagulants are commonly prescribed in patients with kidney disease. Understanding their clinical pharmacology and changes that occur as GFR declines is key to their effective use. Risks and benefits of oral anticoagulants are different in patients with CKD and patients with ESKD. All of these factors must be considered regardless of whether oral anticoagulants are prescribed for FDA-approved indications or used off label. Patients with GFR<30 ml/min per 1.73 m^2, including those on dialysis, were systematically excluded from landmark trials. Extrapolation of comparative efficacy and safety in this patient population is difficult. Warfarin remains the most widely used oral anticoagulant. In our opinion, INR should be closely monitored in patients with ESKD. In our clinical practice, we check INR once a week in patients with ESKD. In our opinion, if the individual time in therapeutic INR range is <50% or if patients experience complications, such as calciphylaxis, we consider switching them to apixaban. Finally, until more data become available, we currently do not use dabigatran, rivaroxaban, and edoxaban in patients with CKD stage 5 and ESKD. Future studies are needed to establish whether use of oral anticoagulants result in net clinical benefit for individuals with CKD stages 4–5 and individuals with ESKD.

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Disclosures

None.

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Erratum

Correction

Nishank Jain and Robert F. Reilly: Clinical Pharmacology of Oral Anticoagulants in Patients with Kidney Disease. *Clin J Am Soc Nephrol* 14: 278–287, 2019.

Due to author error, a correction has been issued for the above referenced article. The text below was incorrectly worded:

"With serum creatinine ≥1.5 mg/dl, age ≥80 years old, or body weight ≤60 kg, a reduced dose of 2.5 mg twice daily is recommended (48)."

The text should have been worded as follows:

The package insert recommends a reduced dose of 2.5 mg twice daily in patients with at least two of the following three clinical characteristics: serum creatinine ≥1.5 mg/dl, age ≥80 years or body weight ≤60 kg.

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Nephropharmacology
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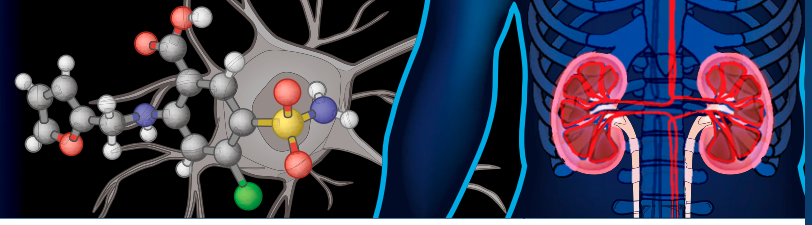

Clinical Pharmacology in HIV Therapy

Mohamed G. Atta,[1] Sophie De Seigneux,[2,3] and Gregory M. Lucas[1]

Abstract

The success of combination antiretroviral therapy in the treatment of HIV-1–positive individuals has shifted clinical attention toward combination antiretroviral drug regimens that optimize tolerability, long-term safety, and durable efficacy. Wherever patients have access to treatment, morbidity and mortality are increasingly driven by non–HIV-associated comorbidities, which may be observed earlier than in age-matched controls and despite the best available combination antiretroviral therapy. Similarly, HIV-1–positive individuals are now diagnosed and treated earlier with anticipated lifelong therapy. The contribution of specific antiretroviral agents to long-term morbidity and mortality is dependent on the pharmacologic characteristics of these agents, and it is increasingly important in this context.

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Introduction

Ever since the first report by the *New York Times* on a mysterious illness in 1981 and the identification of HIV-1 as the cause of this illness in 1983, significant strides have been made in the treatment and management of HIV-1 (Figure 1). Since the introduction of combination antiretroviral therapy in the mid-1990s, there have been >30 agents approved for the treatment of HIV-1–positive individuals.

The HIV life cycle (Figure 2) entails seven steps, including binding, fusion, and entry of virions to the host cell membrane (step 1); release of single-stranded RNA into the cytoplasm (step 2); transcription from RNA to DNA by reverse transcription (step 3); translocation of DNA to the nucleus and integration to the host DNA (step 4); transcription of mRNA coding for viral proteins (step 5); translation to proteins and post-translational cleavage by HIV protease (step 6); and viral maturation and budding (step 7).

There are five main classes of combination antiretroviral therapy drugs (1) that target distinct steps of the HIV-1 cycle. One class contains agents that interfere with viral entry (entry inhibitors) into the cell by binding to viral envelope proteins and preventing attachment and entry into CD4 cells *via* two discrete phases in viral entry: cellular chemokine receptor 5 binding and membrane fusion. A second class contains agents that inhibit viral replication by chain termination after being incorporated into growing DNA strands by HIV-1 reverse transcription (nucleoside reverse transcription inhibitors [NRTIs]). A third class, non-nucleoside reverse transcription inhibitors (NNRTIs), is like NRTIs in that they also interfere with reverse transcription, although they do so by binding reverse transcription at a different site than NRTIs; therefore, they have no cross resistance with the NRTI class. A fourth class (integrase strand transfer inhibitor [INSTIs]) contains agents that inhibit viral DNA insertion into the host cellular genome. A fifth class (protease inhibitors [PIs]) contains agents that inhibit the protease enzyme, which plays a key role in the assembly of the new virus particles.

Despite the plethora of agents targeting distinct stages of HIV-1 cycle (Table 1), current national and international guidelines (2,3) now recommend a combination regimen on the basis of the INSTI drug class in combination with reverse transcription inhibitors (RTIs) as initial therapy for most people with HIV. In certain clinical situations, NNRTIs and PIs coadministered with cytochrome P4503A (CYP3A) inhibitors (pharmacoenhancers) are recommended (2). The fundamental goals of these guidelines are to maximally and durably suppress plasma HIV-1 RNA, restore and preserve immunologic function, reduce HIV-1–associated morbidity and prolong the duration and quality of survival, and prevent HIV transmission (2).

From the kidney standpoint, many of these agents are secreted or cleared by the kidney, requiring dose adjustments in those with compromised kidney function, and they have drug-drug interactions that may increase the effect of adverse reactions, particularly in HIV-1–positive individuals undergoing organ transplantation (4,5). Likewise and equally important, some of these agents have been shown to be directly nephrotoxic, inducing a variety of kidney disorders ranging from AKI, acute interstitial nephritis, kidney stones, crystalline nephropathy, and CKD to proximal and distal tubular kidney dysfunction (1,6–11). Understanding the pharmacologic characteristics of these agents is essential in this context. This concise review focuses on the pharmacologic aspects of the most widely used combination antiretroviral therapy from a nephrocentric viewpoint. Key pharmacologic elements of these agents are shown in Table 2.

Reverse Transcription Inhibitors (RTIs)

Mechanistically, RTIs inhibit transcription of viral RNA into proviral DNA. The class includes NRTIs, for

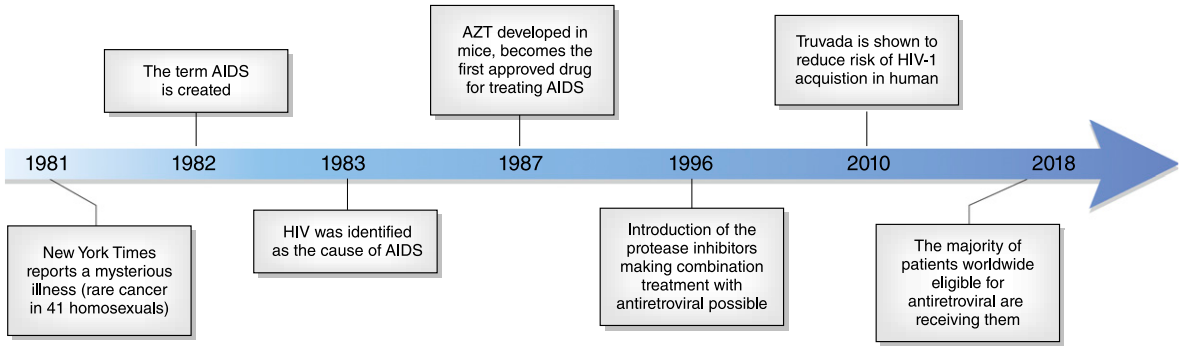

Figure 1. | **Diary of key sentinel timeline events from discovery to evolution of therapy of HIV-1.** AZT, Zidovudine.

which zidovudine is the prototype, and NNRTIs, for which nevirapine is the prototype. In the United States, commercially available NRTIs include abacavir, emtricitabine, didanosine, lamivudine, stavudine, and zidovudine. Tenofovir, which is available as the prodrugs tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF), has a phosphate group bound to the nitrogenous base; as such, these drugs are nucleotide rather than nucleoside analogs. The NRTI class has been historically associated with mitochondrial toxicity, which was once regarded as the most significant adverse effect, with various manifestations, such as hepatic steatosis with lactic acidosis, myopathy, peripheral neuropathy, and lipoatrophy.

Abacavir

Abacavir is a powerful NRTI that has been marketed since 1999. After it is absorbed, abacavir is extensively metabolized, with <2% of an oral dose being excreted into the urine as parent drug. It is metabolized mainly by glucuronidation (36%) and alcohol dehydrogenase (30%) and has a serum $t_{1/2}$ of the active moiety of 21 hours (12). Consequently, abacavir exposure is increased with ethanol use. However, abacavir is associated with no other significant drug interactions, because it is not a significant substrate, inhibitor, or inducer of any members of the CYP family, which makes it an attractive choice for patients receiving other CYP substrates (13). As with other NRTIs, abacavir is phosphorylated intracellularly to an active metabolite. The phosphorylation effectively "traps" the drug within cells. Abacavir administration has been associated with serious and sometimes fatal hypersensitivity reactions. The pathogenesis is related to its binding with high specificity to the HLA-B*5701 protein, changing the shape and chemistry of the antigen binding cleft. This results in a change in immunologic tolerance and the subsequent activation of abacavir-specific cytotoxic T cells, which produce the abacavir hypersensitivity syndrome (14). As such, the presence of the HLA-B*5701 gene allele is associated with elevated odds of developing a hypersensitivity reaction, and screening for this gene allele before prescribing abacavir reduces the incidence to nearly zero (15,16). Abacavir in combination with dolutegravir and lamivudine is one of the initial recommended combination regimens (only for patients who are HLA-B*5701 negative) in most people with HIV (2). In pharmacokinetic studies performed in individuals with CKD with either creatinine clearance <60 ml/min or on hemodialysis who had received abacavir for at least 2 months (17), there were no observed changes in pharmacokinetic parameters. It is, therefore, an attractive choice in patients with CKD.

Lamivudine

Lamivudine is a dideoxynucleoside analog RTI that is frequently combined with other antiretroviral drugs in fixed dose combination tablets. Most of lamivudine is phosphorylated intracellularly to an active metabolite, which has a $t_{1/2}$ of 12–18 hours (18). Kidney clearance is the major route of lamivudine elimination, with a short $t_{1/2}$ of 5–7 hours in the setting of normal kidney function (19). After oral administration, approximately 70% of the total dose is excreted unchanged in the urine by active organic cationic secretion, and only 5%–10% undergoes hepatic metabolism to form a trans-sulphoxide metabolite, which is then also eliminated by the kidney. Interactions with other drugs that are actively secreted *via* the organic cationic transport system (*e.g.*, trimethoprim) should be considered, although lamivudine has few clinically significant drug interactions. The pharmacokinetics of lamivudine are profoundly affected by decreased kidney function. Consequently, dose adjustment is recommended for creatinine clearance <50 ml/min (20). Intermittent hemodialysis does not reduce lamivudine exposure to a clinically significant degree (19). Therefore, after the dose of lamivudine is adjusted to the degree of kidney dysfunction, on the basis of creatinine clearance, no further modification of dose is required for subjects undergoing routine transient (<4 hours) hemodialysis, and supplementary dosing to account for the dialysis session is not required.

Emtricitabine

Emtricitabine is a cytosine nucleoside analog with structural similarity to lamivudine, which allows these agents to be used interchangeably. Less than 4% of emtricitabine binds to human plasma proteins. After a single oral dose, the plasma emtricitabine $t_{1/2}$ is approximately 10 hours, and the drug is mainly eliminated by the kidney by a combination of glomerular filtration and active tubular secretion (21). Emtricitabine is not an inhibitor of human CYP; approximately 86% is recovered in the urine, and 14% is recovered in the feces. No significant drug interactions have been reported with emtricitabine. As

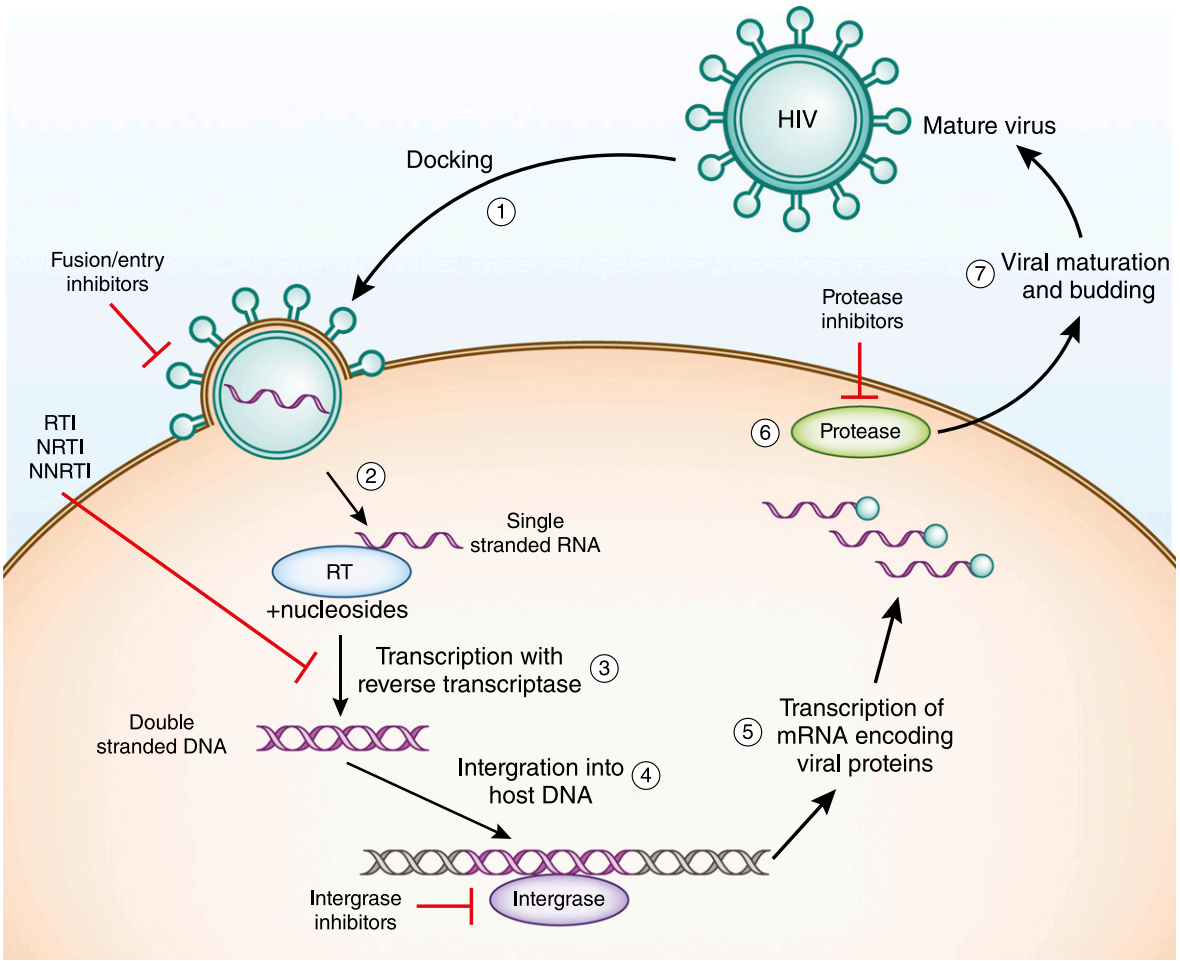

Figure 2. | **Targeting HIV-1.** HIV-1 life cycle and classes of antiretroviral agents that interfere with these specific steps. The seven steps in the HIV lifecycle are identified by numbered circles. Classes of antiretroviral drugs are shown as red lines near the life cycle step that they inhibit. NNRTI, non-nucleoside reverse transcription inhibitor; NRTI, nucleoside reverse transcription inhibitor; RT, reverse transcription; RTI, reverse transcription inhibitor.

shown in Table 1, emtricitabine is one of the most commonly used agents in a number of combined formulations.

Tenofovir Disoproxil Fumarate (TDF)

TDF (Viread) is a prodrug for tenofovir, an acyclic nucleotide diester analog of AMP that acts as a potent competitive inhibitor of HIV-1 and hepatitis B virus reverse transcription. TDF is used alone in monoinfected patients with HBV or in combination with other ARVs for treatment of HIV-1. Combinations include efavirenz/emtricitabine/TDF (Atripla), emtricitabine/rilpivirine/TDF (Complera), and emtricitabine/TDF (Truvada). Because of its high barrier for the development of viral resistance mutations, long plasma and intracellular $t_{1/2}$ (14–17 and >60 hours, respectively), and overall tolerability, TDF is the most widely used antiretroviral agent, although it is substantially being replaced by TAF (discussed below). TDF is rapidly (<1 minute) converted to tenofovir in plasma, and subsequently, it is metabolized intracellularly to the active metabolite, tenofovir diphosphate (TFV-DP), that incorporates into proviral DNA and impairs its transcription (22). TDF does not modify the metabolism of other drugs, and its metabolite tenofovir is primarily eliminated unchanged in urine by both glomerular filtration and active proximal tubular secretion (22). As shown in Figure 3, tenofovir (about 20%–30%) is actively transported across the basolateral membrane into the proximal tubular epithelial cells by organic anion transporters (OATs) (23), with active efflux into the tubular lumen across the apical membrane *via* the multidrug resistance proteins transporters (24). As such, the proximal kidney tubule is the target for tenofovir-associated nephrotoxicities (1,25,26). The pathogenesis of nephrotoxicity is potentially a consequence of effects on the proximal tubule epithelial cell mitochondria and altered mitochondrial cytochrome c oxidase activity (27,28) as well as its downregulatory effect on endothelial nitic oxide synthase, variety of ion transporters, and decreased expression of megalin and cubilin (25,28). Histologically, like other forms of toxic AKI, evidence of proximal tubular injury can be recognized by light microscopy. However, it is the proximal tubular eosinophilic inclusions representing giant mitochondria that are considered distinctive features seen with tenofovir nephrotoxicity (27). By electron microscopy, these changes in proximal tubular cells mitochondria architecture characteristic of tenofovir nephrotoxicity can also be recognized, including

Table 1. Available antiretroviral agents approved for use: Generic names/abbreviations (trade names)

Protease inhibitors
Tipranavir/TPV (Aptivus)
Darunavir + cobicistat (Prezcobix)
Indinavir/IDV (Crixivan)
Atazanavir/ATV (Reyataz)
Atazanavir + Cobicistat (Evotaz)
Darunavir/DRV (Prezzista)
Saquinavir/SQV (Invirase)
Nelfinavir/NFV (Viracept)
Ritonavir/RTV (Norvir)
Lopinavir + Norvir (Kaltera)
Fosamprenavir/FPV (Lexiva)
Integrase inhibitors
Raltegrivir/RAL (Isentress)
Doultegravir/DTG (Tivicay)
Elvitegravir/EVG (Vitekta)
Bictegravir/BIC
Fusion/entry inhibitors
Enfuviritide/ENF (Fuzeon)
Maraviroc/MVC (Selxentry)
Multiclass single-tablet drug combination
Efavirenz + emtricitabine + tenofovir disoproxil fumarate, EFV/FTC/TDF (Atripla)
Emtricitabine + rilpivirine + tenofovir disoproxil fumarate, FTC/RPV/TDF (Complera)
Elvitegravir + cobicistat + emtricitabine + tenofovir disoproxil fumarate, EVG/COBI/FTC/TDF (Stribild)
Rilpivirine + tenofovir alafenamide fumarate + emtricitabine, RPV/TAF/FTC (Odefsey)
Elvitegravir + cobicistat + emtricitabine + tenofovir alafenamide fumarate, EVG/COBI/FTC/TAF (Genvoya)
Bictegravir + emtricitabine + tenofovir alafenamide fumarate, BIC/FTC/TAF (Biktarvy)
Abacavir + dolutegravir + lamivudine, ABC/DTG/3TC (Triumeq)
Dolutegravi + rilpivirine, DTG/RPV (Juluca)
Dolutegravir + emtricitabine + tenofovir alafenamide fumarate, DTG/FTC/TAF
Nucleoside/nucleotide analogs (NRTIs)
Lamivudine + zidovudine, 3TC/ZDV (Combivir)
Abacavir/ABC (Ziagen)
Emtricitabine/FTC (Emtriva)
Tenofovir disoproxil fumarate/TDF (Viread)
Emtricitabine + tenofovir disoproxil fumarate, FTC/TDF (Truvada)
Tenofovir alafenamide fumarate/TAF (Vemlidy)
Lamivudine/3TC (Epivir)
Abacavir sulfate + Lamivudine, ABC/3TC (Epzicom)
Abacavir sulfate + Lamivudine + Zidovudine, ABC/3TC/ZDV (Trizivir)
Stavudine/d4T (Zerit)
Didanosine/DDI (Videx, Videx EC)
Zidovudine/AZT/ZDV (Retrovir)
Non-nucleosides (NNRTIs)
Rilpivirine/RPV (Edurant)
Etravirine/ETV (Intlence)
Delavirdine/DLV (Rescriptor)
Efavirenz/EFV (Sustiva)
Nevirapine/NVP (Viramune)
Pharmacoenhancer
Ritonavir/RTV (Norvir)
Cobicistat/COBI (Tybost)

NRTI, nucleoside reverse transcription inhibitor; NNRTI, non-nucleoside reverse transcription inhibitor.

autophagosomes and dysmorphic mitochondria of variable sizes, shapes, and incomplete cristae (27,29). Use of TDF with PIs, such as atazanavir or ritonavir, increases TDF drug concentrations and boosts its potential for nephrotoxicity and incident CKD (8). Other risk factors for TDF-induced proximal tubular injury include aging, immunodeficiency, diabetes mellitus, preexisting kidney disease, polymorphisms of transporters involved in drug secretion by the kidney, prolonged exposure, and concomitant use of didanosine or PIs (5,7,30). Severe proximal tubular injury may progress to eGFR decline, osteomalacia, and pathologic fractures. As such, guidelines have recommended avoiding TDF use in HIV-1–positive people who have a GFR<60 ml/min per 1.73 m^2 (4). No studies have specifically examined the safety of continued TDF use in individuals with evidence of proximal tubular dysfunction but preserved eGFR. Consequently, in TDF-treated individuals who experience a confirmed eGFR decline by >25% from baseline and to a level <60 ml/min per 1.73 m^2, it is recommended to substitute alternative antiretroviral drug(s) for TDF, particularly in those with evidence of proximal

Table 2. Key clinical pharmacologic aspects of commonly used antiretroviral agents

Drug	Elimination/$t_{1/2}$	Plasma Protein Binding	Metabolism	Dose in CKD and Dialysis	Nephrotoxicity Potential
Reverse transcription inhibitors					
Abacavir	85% by the kidney $t_{1/2}$ 1.5 h for the parent drug and 21 h for the active moiety	50%	Glucuronidation (36%) Alcohol dehydrogenase (30%)	No dose adjustment	Acute interstitial nephritis
Lamivudine	Primarily by the kidney *via* organic cation transporter secretion $t_{1/2}$ 5–7 h	Low <36%	Minor, only 5% of drug	Dose adjustment for Cr. Cl. <50 ml/min, reduce both first and maintenance dose on dialysis No significant clearance by HD or CAPD/APD	Rare
Emtricitabine	86% by the kidney $t_{1/2}$ 8–10 h	Low <4%	No significant metabolism	Dose adjustment for Cr. Cl. <50 ml/min	Rare
Tenofovir disoproxil fumarate	70%−80% by the kidney $t_{1/2}$ 14–17 h	<7%	Hydrolysis (by non-CYP enzymes) intracellularly to tenofovir	Dose adjustment for Cr. Cl. <50 ml/min 300 mg every 48 h for Cr. Cl. 30–50 ml/min, twice weekly for 10–29 ml/min, once weekly on dialysis Guidelines do not recommend using with eGFR<60 if possible 10% of the administered 300 mg tenofovir disoproxil fumarate dose is removed by 4 h of dialysis	Acute kidney disease and CKD, Fanconi syndrome, nephrogenic diabetes insipidus
Tenofovir alafenamide fumarate	1% excreted in the urine and 31.7% excreted in feces $t_{1/2}$ 90 min	80%	>80 is metabolized intracellularly with Cathepsin Ab in PBMCs and CES1 in hepatocytes CYP3A (minimal)	None for Cr. Cl. >30 ml/min Not recommended for Cr. Cl. <30 ml/min	Proximal tubular cell injury has been reported
Integrase strand transfer inhibitors					
Raltegravir	9% unchanged by the kidney, the rest are metabolites recovered in feces (50%) and urine $t_{1/2}$ approximately 9 h	83%	UGT1A1	No dose adjustment No data on dialysis clearance	Rare
Elvitegravir	95% is recovered in feces (hepatobiliary excretion) $t_{1/2}$ approximately 3 h $t_{1/2}$ approximately 9 h when boosted with ritonavir or cobicistat	>99%	CYP3A4 (major); UGT1A1/3 (minor)	No dose adjustment No data on dialysis clearance, but it is unlikely to be dialyzable	Rare
Dolutegravir	53% is excreted unchanged in feces, <1% by urine, 31% of metabolites in urine $t_{1/2}$ 11–12 h	>99%	UGT1A1 (major) CYP3A (minor)	No dose adjustment, not removed by dialysis	Rare
Pharmacoenhancers					
Cobicistat	86% excreted in feces, 8% in urine $t_{1/2}$ 3–4 h	98%	CYP3A (major) CYP2D6 (minor)	Avoid elvitegravir/cobicistat/tenofovir disoproxil fumarate when Cr. Cl. <70 ml/min Avoid elvitegravir/cobicistat/tenofovir alafenamide fumarate when Cr. Cl. <30 ml/min	Rare
Ritonavir	86% in feces $t_{1/2}$ 3–5 h	98%–99%	CYP3A (major) CYP2D6 (minor)	No dose adjustment	AKI, CKD, increased risk of tenofovir disoproxil fumarate nephrotoxicity

Cr. Cl., creatinine clearance; HD, hemodialysis; CAPD, continuous ambulatory peritoneal dialysis; APD, automated peritoneal dialysis; CYP, cytochrome P; CES1, carboxylesterase 1; UGT, uridine glucuronosyl transferase; PBMCs, peripheral blood mononuclear cells.

tubular dysfunction, such as euglycemic glycosuria or increased urinary phosphorus excretion, hypophosphatemia, or new-onset or worsening proteinuria (4).

It is generally recommended that TDF be dosed once weekly in HIV-positive individuals on maintenance hemodialysis. However, a recent pharmacokinetic study determined that once weekly dosing with hemodialysis resulted in steady-state plasma and intracellular peripheral blood mononuclear cell (PBMC) concentrations that are higher than those found in patients with normal kidney

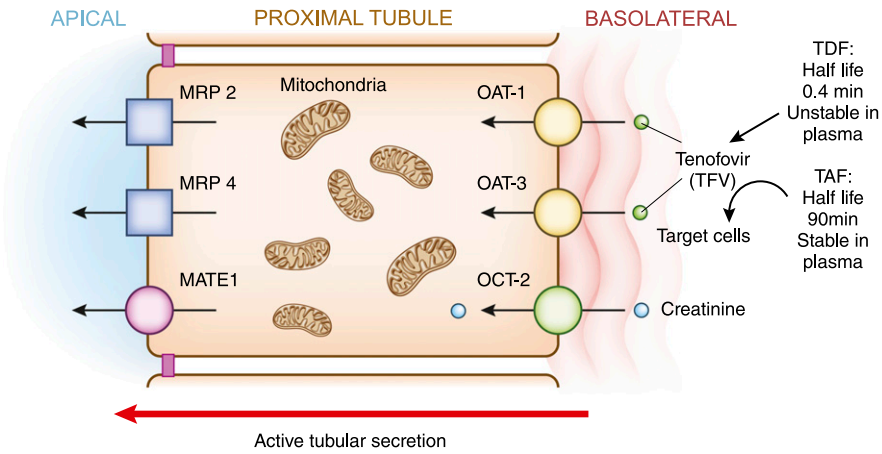

Figure 3. | **The proximal kidney tubule is the target for tenofovir-associated nephrotoxicities.** Handling of tenofovir (TFV), the active metabolite of tenofovir disoproxil fumarate (TDF) and tenofovir alafenamide fumarate (TAF), by the proximal tubular cells of the kidney. TFV exits the tubular circulation primarily *via* the organic anion transporter 1 (OAT1) on the basolateral membrane, and after it is within the cell, it exits into the urine *via* the apical multidrug resistance protein type 4 (MRP 4) and possibly, MRP 2. TAF is more stable in plasma than TDF, with minimal hydrolyses to TFV. The bulk of TAF is rather transported to target cells. MATE1, multidrug and toxin extrusion transporter 1; OCT2, organic cation transporter 2.

function who are taking TDF daily (31). This suggests that less frequent dosing of TDF may be appropriate in patients on dialysis, but further evaluation is required.

Tenofovir Alafenamide Fumarate (TAF)

TAF (formerly GS-7340) is the next generation tenofovir prodrug that has a distinct metabolism, and it was designed to maximize antiviral potency and clinical safety. The Tmax of TAF is approximately 2 hours, and compared with TDF, TAF is much more stable in the plasma, with a $t_{1/2}$ of 90 minutes. This is related to the presence of a phenol and an alanine isopropyl esther in its structure. TAF penetrates inside cells, where cathepsin A hydrolyses it to tenofovir, which is subsequently phosphorylated to TFV-DP (32). This results in higher intracellular concentrations of the active phosphorylated moiety TFV-DP and lower circulating concentrations of tenofovir relative to TDF. Improved kidney safety is likely attributable to lower circulating plasma concentrations of tenofovir. The hydrolysis of TAF within cells is more rapid compared with TDF, and its $t_{1/2}$ within T cells is 28 minutes. A radiolabeled distribution study in dogs showed that, on a dose per dose basis, TAF administration leads to an increased distribution of tenofovir to tissues of lymphatic origin compared with TDF (33). Because tenofovir is actively transported from the blood into proximal tubule kidney cells by OAT1 and OAT3, a reduction in plasma exposures of tenofovir may result in lower concentrations in proximal tubule cells and less nephrotoxicity (34). In addition, there is no evidence of proximal tubular kidney cell uptake of TAF *via* OAT1 and OAT3, suggesting less tubular cell accumulation and nephrotoxicity (35). Thus, an optimized dose of TAF could result in improved clinical efficacy and long-term safety relative to TDF. TAF dosing at 25 mg has substantially reduced tenofovir exposures, with improved pharmacodynamics compared with 300 mg TDF (36). Compared with 300 mg TDF, TAF showed more potent antiviral activity, higher PBMC intracellular TFV-DP concentrations, and lower plasma tenofovir exposures at approximately 1/10th of the dose. Administration of TAF 25 mg leads to higher intracellular concentrations of TFV-DP in PBMCs and 86% lower plasma concentrations of tenofovir than TDF 300 mg. TAF is excreted mainly in the urine and feces, predominantly as tenofovir (36). Both drugs were compared in randomized phase 2 and phase 3 studies. In HIV-naïve patients, TAF and TDF showed a similar efficacy for viral control at 48 weeks. However, TAF was associated with a favorable proximal tubular kidney injury profile and a smaller decrease in eGFR compared with TDF (37). Similar observations were made in experienced patients in switch studies, where TAF replaced TDF (38). Despite the favorable kidney safety indicators from large clinical trials, TAF may potentially be nephrotoxic in persons with comorbid conditions, such as chronic liver disease and diabetes mellitus, as recently reported (29). Consequently, longitudinal follow-up studies will be required to ascertain the nephrotoxicity potential, if any, of TAF and its beneficial effect over TDF (39). TAF metabolites are excreted in the urine and feces, and dose adjustment is not required in CKD when the creatinine clearance is 30 ml/min or higher. In a small study of patients with clearances lower than 30 ml/min, TAF plasma exposure increased only moderately. However, the drug has not been evaluated in patients on dialysis. TAF is used in multiple single-tablet combinations, including Genvoya (elvitegravir, cobicistat, emtricitabine, and TAF), Odefsey (emtricitabine, rilpivirine, and TAF), and Descovy (emtricitabine and TAF).

TAF, like TDF but to a lower extent, is a substrate of P-glycoprotein (P-gp) and human breast cancer resistance protein (BCRP). As such, inhibitors of BRCP and P-gp have a lower influence on TAF compared with TDF, and inhibitors of these proteins may be used with TAF if needed. An example of this is ledipasvir, an agent that inhibits the nonstructural gene component of hepatitis C (NS5A) involved in replication pathways of the virus,

which is used in combination with sofosbuvir for the treatment of chronic hepatitis C, a commonly encountered comorbidity in HIV-1–positive individuals. Ritonavir and Cobicistat will increase TAF plasma levels approximately twofold *via* the inhibition of the intestinal P-gp (40). It is recommended that the 10-mg dose of TAF be used when administered with a boosted PI (cobicistat or ritonavir), whereas the 25-mg dose is safe when combined with NNRTIs or INSTIs. Although TAF is not considerably metabolized by CYP, it is not recommended to use with CYP or P-gp inducers.

Iintegrase Strand Transfer Inhibitor (INSTIs)

INSTI coadministered with two NRTIs is now the most common first-line strategy for naïve HIV-1–positive individuals recommended by the US Department of Health and Human Services adult and adolescent HIV treatment guidelines (2). The transition from NNRTI- and PI-based regimens to INSTI-based ones was driven by improved efficacy, safety, and tolerability profiles and fewer drug-drug interactions, including the CYP3A4-drug interactions. Consequently, these agents, in combination with RTIs, are the preferred antiretroviral agents to use in HIV-positive individuals undergoing organ transplantation (21). There are four agents in this class, and the first clinically available agent, raltegravir, was approved in 2007. This was followed by approval of the second generation INSTIs elvitegravir in 2012, dolutegravir in 2013, and most recently, bictegravir in 2018. They act by inhibiting viral DNA incorporation into the host genome (41).

Raltegravir

Raltegravir is a first generation INSTI that characteristically has highly variable pharmacokinetics both between patients and within the same patients on different days (42), dictating twice daily dosing (43). Raltegravir is metabolized by glucuronidation, primarily by uridine glucuronosyl transferase 1A1 (UGT1A1) (44).

Elvitegravir

Compared with raltegravir and dolutegravir, which possess minimal CYP involvement, elvitegravir metabolism occurs primarily *via* CYP3A4 and requires pharmacokinetic boosting to achieve systemic exposures that permit once daily dosing. Consequently, elvitegravir is coformulated with cobicistat (either as elvitegravir/cobicistat/TDF/emtricitabine or elvitegravir/cobicistat/TAF/emtricitabine) or must be used with ritonavir.

Dolutegravir

Dolutegravir is highly potent and dissociates more slowly from integrase-DNA complexes than first generation INSTIs. Dolutegravir is readily absorbed, with Tmax of 0.5–2 hours. Its $t_{1/2}$ is 11–12 hours in HIV-1–positive individuals. The drug is mainly protein bound, and it is a substrate for P-gp and BCRP. Dolutegravir is predominantly metabolized in the liver *via* UGT1A1, and its urinary excretion is <1% (45,46). Multiple drugs interact with dolutegravir by altering UGT1A1, such as some NNRTIs (EFV, DRV, ATV, *etc.*), but no significant interaction has been described with TDF or TAF (47). Although it has no reported effect on the CYP system or drug transporters, dolutegravir inhibits organic cation transporter 2, which is responsible for creatinine uptake at the basolateral membrane of the proximal tubular kidney cells as shown in Figure 4 (48). As such, dolutegravir has been shown to raise serum creatinine by up to 0.4 mg/dl (44 μmol/L) with predictable decrease in eGFR by 10–15 ml/min per 1.73 m^2 without altering true GFR (49). Under steady state, such change may be manageable in those with normal kidney function but could be challenging in those with underlying CKD. However, no kidney toxicities have been described with the use of this agent. Given its hepatic metabolism, no dose adjustment is required in those with kidney disease. However, dolutegravir exposure may be decreased by severe kidney impairment (50). Although it has not been systematically evaluated in those receiving kidney replacement therapy, given its high protein binding, it is not expected to be removed by dialysis (51). Dolutegravir is an attractive choice for HIV-1–positive individuals undergoing organ transplantation given the lack of documented interactions with calcineurin inhibitors (30).

Protease Inhibitors (PIs)

Because of lipodystrophy, which is manifested by lipoatrophy and/or lipid accumulation in the trunk, the use of PIs as part of combination antiretroviral therapy has significantly declined. Another major limiting toxicity is the high incidence of crystallization within kidney tubules and nephrolithiasis with one of the most potent PIs, indinavir (9) in addition to unconjugated hyperbilirubinemia and nephrolithiasis with atazanavir use. Risk factors for nephrolithiasis with the use of indinavir and atazanavir include alkaline pH, low lean body mass, using higher doses, adding a pharmacologic boosting agent, warm climates, and suboptimal daily fluid intake (1). Both agents are also associated with significant tubulointerstitial disease and increased risk for incident CKD (52). The use of atazanavir in conjunction with ritonavir as a booster has the potential of increasing the risk for the development of granulomatous interstitial nephritis (53–55). Similar to pharmacoenhancers, these agents are not recommended in those undergoing organ transplantations because of the significant drug-drug interactions with calcineurin inhibitors and mammalian target of rapamycin inhibitors (5,56). Likewise, awareness of other potential drug interactions with these agents is critical in predicating safety and efficacy of other concomitantly administered drugs. Nephrologists are encouraged to use resources dealing with HIV-specific drug interactions, such as www.hiv-druginteractions.org, for up to date information.

Pharmacoenhancers

Cobicistat

Cobicistat is used as an inhibitor of CYP, leading to higher plasma concentrations of antiretrovirals metabolized by this enzyme. It has no direct antiretroviral activities in contrast to ritonavir (which is also used principally for its pharmacoenhancer properties), but the inhibitory effect of cobicistat on CYP is like the one obtained with ritonavir.

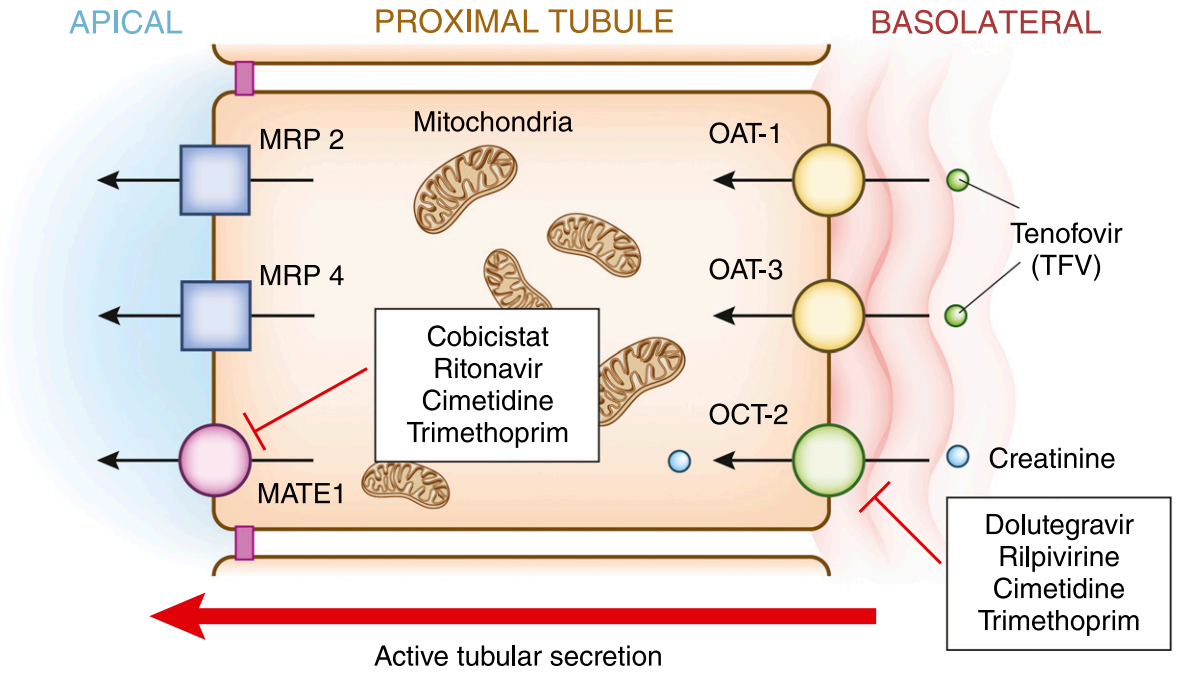

Figure 4. | Agents that interfere with creatinine secretion in proximal tubule raising its actual serum value. Creatine is secreted at the basolateral membrane *via* the organic cation transporter 2 (OCT2), and both dolutegravir and rilpivirine and commonly used drugs compete with this process. Creatinine exits the proximal tubular cells *via* multidrug and toxin extrusion transporter 1 (MATE1). Pharmacoenhancers cobicistat and ritonavir compete with this step as well as other drugs. MRP 2, multidrug resistance protein type 2; MRP 4, multidrug resistance protein type 4; OAT1, organic anion transporter 1; OAT3, organic anion transporter 3; TFV, tenofovir.

Cobicistat is, however, more specific for CYP3A than ritonavir, with a lower effect of CYP2D6. It also inhibits P-gp, BCRP, OATP1B1, and OATP1B3 transporters. It is used in conjunction with other antiretroviral drugs as a booster to increase their concentrations (57). Cobicistat is mainly protein bound with a $t_{1/2}$ of approximately 3–4 hours, and it is primarily excreted in the feces, with only 8% in the urine (58). Given its intended pharmacokinetic effects, cobicistat interacts with numerous drugs metabolized by CYP3A4, 2D6, or P-gp and should not be administered with CYP3A4 enhancers. It increases TAF level approximately twofold *via* the inhibition of intestinal P-gp, and TAF dose is reduced to 10 mg in cobicistat-containing regimens. Although it has no kidney toxicities, it inhibits creatinine secretion at the apical membrane of the proximal tubular kidney cells by primarily inhibiting multidrug and toxin extrusion transporter 1 and OAT1B1–3. It is, therefore, associated with an average 13% (approximately 10 ml/min) decline in eGFR with no actual kidney injury (59). The rise of serum creatinine with cobicistat is more prominent compared with ritonavir due to its greater inhibition of multidrug and toxin extrusion transporter 1 (60).

No dose adjustment is required in CKD. However, in its coformulated tablet elvitegravir/cobicistat/TDF/emtricitabine, it is not recommended in those with creatinine clearance of <70 ml/min and should be discontinued in those with creatinine clearance of <50 ml/min. With the introduction of TAF, the coformulated tablet elvitegravir/cobicistat/TAF/emtricitabine can be used in those with creatinine clearance of 30–69 ml/min (38). There is no experience with this drug at lower levels of kidney function, and drug-drug interactions have not been evaluated (61).

Ritonavir (Norvir)

Ritonavir, like other PIs (except for nelfinavir), is metabolized by CYP3A4 (major) and CYP2D6 (minor) with a serum $t_{1/2}$ of 3–5 hours. It is also a strong inhibitor of CYP3A4 (62) and induces its own metabolism (63). However, it is rarely used at doses needed for antiretroviral activity due to near-universal gastrointestinal side effects. Rather, ritonavir is used at low doses with other PIs as a pharmacokinetic enhancer or "booster" to increase concentrations and decrease dosing frequency of other agents.

Conclusions

The landscape of combination antiretroviral therapy has progressed markedly over the past 30 years, and it will continue to expand with the potential future introduction of injectable long-acting agents or the preventive treatment with broadly neutralizing HIV antibody therapy, which are both currently under clinical testing. This will likely present a new set of challenges to providers and nephrologists who are required to keep themselves abreast with such an evolving field.

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Disclosures

None.

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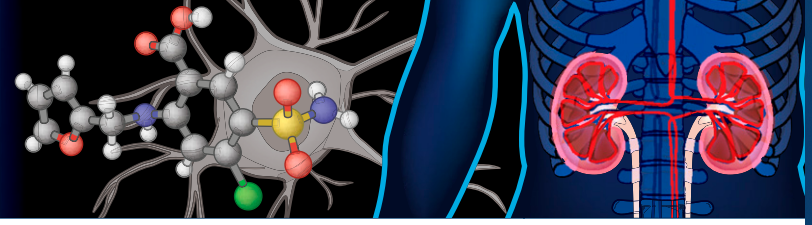

Estimation of Kidney Function in Oncology
Implications for Anticancer Drug Selection and Dosing

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Abstract
Estimation of kidney function in patients with cancer directly affects drug dosing, agent selection, and eligibility for clinical trials of novel agents. Overestimation of kidney function may lead to overdosing or inappropriate agent selection and corresponding toxicity. Conversely, underestimation of kidney function may lead to underdosing or inappropriate agent exclusion and subsequent therapeutic failure. It would seem obvious that the most accurate estimates of kidney function should be used to reduce variability in decision making and ultimately, the therapeutic outcomes of toxicity and clinical benefit. However, clinical decision making is often more complex. The Cockcroft–Gault formula remains the most universally implemented estimator of kidney function in patients with cancer, despite its relative inaccuracy compared with the Chronic Kidney Disease Epidemiology Collaboration equation. The Chronic Kidney Disease Epidemiology Collaboration equation is a more precise estimator of kidney function; however, many currently used kidney function cutoff values were determined before the development of the Chronic Kidney Disease Epidemiology Collaboration equation and creatinine assay standardization using Cockcroft–Gault estimates. There is a need for additional studies investigating the validity of currently used estimates of kidney function in patients with cancer and the applicability of traditional anticancer dosing and eligibility guidelines to modern and more accurate estimates of kidney function. In this review, we consider contemporary calculation methods used to estimate kidney function in patients with cancer. We discuss the clinical implications of using these various methods, including the potential influence on drug dosing, drug selection, and clinical trial eligibility, using carboplatin and cisplatin as case studies.

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Introduction
Patients with cancer often receive multiple narrow therapeutic index drugs, many of which are eliminated by the kidneys and therefore, exhibit decreased clearance in patients with impaired kidney function. Anticancer drugs are no exception; these drugs are highly toxic with narrow therapeutic indices. Their adverse effects are often severe, but they are typically manageable when patient exposure to the drug is prospectively estimated and doses are adjusted accordingly. Thus, accurate patient-specific dosing and agent selection on the basis of drug clearance and exposure are vital to ensure safety while maintaining anticancer activity.

Quantitative estimates of kidney function have been used for decades to guide patient suitability, drug selection, and dose adjustments for anticancer agents cleared by the kidney. Kidney function estimates are also used to determine eligibility for clinical trials of novel agents. This process is not without risk. Overestimation of kidney function may lead to overdosing or inappropriate agent selection, lower than expected clearance of the drug, and an unanticipated increase in systemic exposure, leading to a corresponding increase in toxicity. Conversely, underestimation of kidney function may lead to underdosing or inappropriate agent exclusion, higher than expected clearance of the drug, and an unanticipated decrease in systemic exposure, leading to therapeutic failure. Therefore, accurate and clinically practical estimates of kidney function are required to optimize clinical outcomes in all patients but especially those receiving anticancer agents for which the adverse effect profile can be severe and maximal dosing may be important to optimize anticancer response.

In this review, we present contemporary bedside calculation methods used to estimate kidney function in the population of patients with cancer. The clinical implications of using various estimates of kidney function in these patients, including the potential influence on drug dosing decisions, agent suitability, and eligibility for clinical trial enrollment, are discussed. Finally, the effect of the most recent Food and Drug Administration (FDA) draft guidance regarding pharmacokinetic studies in patients with impaired kidney function is explored.

Kidney Function Estimates in the General Population
GFR is routinely used to quantify kidney function and diagnose CKD. GFR may be measured (measured GFR [mGFR]) directly by determining clearance of exogenous markers, such as inulin, radioactive agents (^{51}Cr-EDTA), or radiocontrast agents (iothalamate and iohexol),

although this is not clinically practical due to time, cost, and convenience. More commonly, GFR is estimated (eGFR) on the basis of endogenous serum creatinine (SCr) values (1–3). Implementation of isotope dilution mass spectrometry-traceable standardization of SCr assays in 2010 has led to reduced interlaboratory variability and improved consistency in SCr measurements in the United States (1). One method of determining kidney function has been to use creatinine clearance (CrCl), reported in milliliters per minute, as a surrogate for GFR. CrCl can be measured (measured creatinine clearance [mCrCl]) by 12- or 24-hour urine collections, but this method is time consuming and inconvenient. The Cockcroft–Gault (CG) formula was published in the 1970s as a bedside equation for estimated creatinine clearance (eCrCl). However, this equation is an imprecise estimate of true GFR in large part due to its failure to adequately compensate for several non-GFR determinants of SCr, including body composition, diet, age, sex, race, tubular secretion, and extrarenal elimination of creatinine, as well as the original study's reliance on mCrCl by 24-hour urine collection as a surrogate for true GFR (1,4,5). Additionally, after the isotope dilution mass spectrometry standardization of SCr assays, eGFR values decreased by 10%–20% compared with nonstandardized values, further placing the accuracy of the CG formula into question in conjunction with the widespread modern use of standardized SCr values (1). Despite these limitations and its small and nondiverse study population (a subselection of mostly men and all white patients) (6), the CG formula has been widely adopted into clinical practice due to its convenience and perceived accuracy. Since its incorporation into the 1998 FDA guidance on pharmacokinetics for patients with impaired kidney function, the CG formula has become the most common measure by which recommendations for kidney function-based drug dosing and agent selection are made (1,7).

Improved methods for determining eGFR have been developed in the last 20 years, notably the several iterations of the Modification of Diet in Renal Disease (MDRD) Study equation (MDRD-4 and MDRD-6) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and the CKD-EPI cystatin C equations (1,3,5,8,9). These equations report eGFR indexed for body surface area (BSA) in milliliters per minute per 1.73 m^2. Importantly, when comparing kidney function estimates within individuals, the estimates must be expressed in equivalent units. Therefore, estimation of a patient's absolute eGFR in units of milliliters per minute (nonindexed for BSA) must be performed by multiplying the indexed eGFR value by (patient's BSA/1.73 m^2). This allows for a direct comparison of absolute eGFR as calculated by the CKD-EPI equation or the MDRD equation, with CrCl by achieving congruent units (milliliters per minute) between the two measures. These equations were developed with standardized SCr values and iothalamate clearance as the reference, and they incorporate easily measured surrogates (age, sex, and race) to account for the effects of some non-GFR determinants of SCr. Use of these equations results in a value that is closer to the true GFR compared with the CG formula, especially for older patients (1,3). The CKD-EPI equation is recommended for use in routine clinical practice by the Kidney Disease Improving Global Outcomes and the National Kidney Foundation-Kidney Disease Outcomes Quality Initiative (NKF-KDOQI) guideline groups, but this recommendation has not yet been fully adopted by many non-nephrology specialties, including oncology (10–12) (Table 1).

Kidney Function Estimates in Patients with Cancer

Patients with cancer commonly present with underlying impaired kidney function. Over one half and up to one fifth of patients with solid tumors have eCrCl (milliliters per minute) or eGFR (milliliters per minute per 1.73 m^2) measures of <90 and <60, respectively (2,13). These numbers likely underestimate the true prevalence of decreased GFR in patients with cancer, because the studies from which they were derived excluded patients with hematologic malignancies, diseases that are associated with a high prevalence of kidney impairment. Importantly, use of SCr in isolation (*i.e.*, assessment of eligibility for treatment defined as SCr<1 or 1.5 times the upper limit of normal) typically overestimates kidney function, with about 60% of patients with "normal" SCr values presenting with decreased kidney function. In fact, 5%–15% of patients with eCrCl (milliliters per minute) or eGFR (milliliters per minute per 1.73 m^2) <60 present with "normal" SCr values (2,13). Moreover, the high toxicity of anticancer drugs and fatal consequences of the disease if treated ineffectively underscore the need for routine and accurate estimation of GFR to optimize drug safety and efficacy. The older age of patients with cancer portends additional risk, because it is associated with a normal age-related decline in kidney function as well as increased risks of developing a malignancy, suffering cancer-related death, and experiencing chemotherapy-related toxicity (4,14,15). Therefore, it is essential that estimates of kidney function can maintain accuracy in this older patient subpopulation.

Kidney function plays a large role in determining anticancer therapy, including anticancer agent selection, dosing, and eligibility for investigational drugs and clinical trials, and thereby, it affects clinical outcomes of patients with cancer. Although definition of the appropriate way to estimate kidney function is important to the dosing of many drugs within the general medical population, it is particularly crucial in patients with cancer due to the highly toxic adverse event profiles and often steep dose-therapeutic response relationships that characterize anticancer agents as a class. Typically, anticancer drug dosing is on the basis of the maximum tolerated dose, which is the highest dose that may be administered without unacceptable toxicity, to maximize anticancer efficacy. Dose reductions or alternative agent selection due to decreased eGFR may lead to reduced effectiveness, failure of therapy, use of less effective or more toxic second- or third-line agents, and ultimately, decreased survival. Investigational oncology drug clinical trials offer patients with advanced-stage, relapsed, and refractory cancer potentially effective novel therapeutics, but many require minimum kidney function thresholds for enrollment. Patients with cancer may benefit from aggressive anticancer regimens. Therefore, underestimation of true kidney function may unnecessarily preclude patients from more effective agents, higher doses, or clinical trial enrollment and thereby, potentially worsen outcomes. Conversely, overestimation of kidney

Table 1. Comparison of bedside equations used to estimate kidney function

Variables	Measures	Study Population Demographics	Study Population Kidney Function	Advantages	Limitations
CG (1976)					
Age, SCr, sex, weight	eCrCl, ml/min	*n*=236 (subpopulation of 534 patients on the basis of duplicate 24-h mCrCl being within 20%)	Average CrCl approximately 78 ml/min	Convenient to use	Estimates creatinine clearance as a surrogate for GFR
		Mean age 53 yr, 24% >70 yr, 96% men		Model used for determining recommendations for drug dose adjustment for kidney function	Correlation between mCrCl and eCrCl R^2=0.69
		Veterans Hospital patients			Uses 24-h urine collection as standard
					Does not use standardized SCr laboratory values, and eGFRs before standardization were 10%–20% higher
					Underestimates at severely reduced kidney function
					Less accurate in patients with extremes of age or body size
					Adjustment for sex is empirical
MDRD (2006)					
Age, SCr, sex, race	eGFR, ml/min per 1.73 m^2	*n*=1628	Average GFR 39.8 ml/min per 1.73 m^2	P30 values range 73%–93%	Underestimates at normal and mildly reduced kidney function (>60 ml/min)
		Mean age 50.6 yr	Few patients with GFR>90 ml/min per 1.73 m^2	Uses iothalamate clearance as standard	Not used for determining most kidney drug-dosing recommendations
		60% men		MDRD-4 uses standardized SCr laboratory values	
		88% white		Improves on CG estimation at GFR<60 ml/min per 1.73 m^2	
		6% diabetic			
		Patients with CKD			
CKD-EPI (2009)					
Age, SCr, sex, race	eGFR, ml/min per 1.73 m^2	*n*=5253	Mean GFR 68 ml/min per 1.73 m^2	P30=91.5% with cystatin C	Not used for determining most kidney drug-dosing recommendations
		Mean age 43 yr, 13% >65 yr		Uses iothalamate clearance as standard	
		58% men		Uses standardized SCr laboratory values	
		63% white, 32% black, 1% Asian		Improves on MDRD estimation at GFR>60 ml/min per 1.73 m^2	
		Patients with CKD			

CG, Cockcroft–Gault; eCrCl, estimated creatinine clearance; mCrCl, measured creatinine clearance; CrCl, creatinine clearance; SCr, serum creatinine; MDRD, Modification of Diet in Renal Disease; P30, percentage of estimates that were within 30% of the reference value; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

function may put patients with cancer at unnecessary risk for major organ toxicity from narrow therapeutic index anticancer drugs cleared by the kidneys (4,14,15). Most patients with cancer and impaired kidney function have stage 2 or 3 (eGFR=60–89 and 30–59 ml/min per 1.73 m^2, respectively) kidney disease (approximately 40%–50% and 15%–20% of all patients with cancer, respectively) according to NKF-KDOQI classification (2,11,13). These two stages straddle many important drug dose, drug selection, and clinical trial enrollment thresholds (16–18).

The process of deciding which kidney function estimate to implement in modern oncology practice remains complicated. Many anticancer drug cutoffs were determined before the development of the CKD-EPI equation using CG estimates of kidney function and before creatinine assay standardization in 2010. Although it has been firmly established that the CKD-EPI equation is superior to the CG formula in estimating GFR, the real clinical question that needs to be answered is the method of assessing kidney function that is best suited to dose adjust anticancer agents for kidney function. Important considerations include the accuracy of the model as it relates to estimation of kidney function in the individual patient and the kidney function model used to determine unacceptable toxicity when the chemotherapeutic agent was developed. Additionally, one must evaluate the risk-benefit scenario (*i.e.*, the potential severity and complications of adverse effects when overdosing versus potential therapeutic failure when underdosing). There may be clinical scenarios in which the use of the CG formula may be preferable, despite its decreased precision and accuracy in the estimation of GFR. Admittedly, one of the weaknesses of using GFR to dose drugs is that it does not account for the contribution of tubular secretion to drug clearance, which can be significant for some drugs. Unless a drug has a secretion profile similar to that of creatinine, neither eCrCl- nor creatinine-based estimates of GFR are good representations of that drug's net kidney clearance. However, the fact remains that the CKD-EPI equation provides an eGFR that is closer to true GFR than eCrCl. Accurate estimations of kidney function are imperative for optimizing anticancer efficacy while avoiding unacceptable toxicity in patients with cancer, especially the elderly, in whom both decreased kidney function and malignancies are more common.

Several clinical oncology groups, including the International Society of Geriatric Oncology (SIOG) and the National Comprehensive Cancer Network (NCCN), recommend an assessment of kidney function to adjust dose and reduce toxicity in patients before chemotherapy, even when SCr is within the normal range. However, there are currently no universal guidelines stating which method of estimating kidney function is preferred in patients with cancer. The NCCN vaguely recommends use of CrCl in their guidelines pertaining to elderly adults and "GFR calculations" in their guidelines related to adolescent and young adults, whereas the SIOG does not state a preferred estimation method (4,14,19,20). Most currently published models of estimating kidney function and all of those regularly used in clinical practice are derived from populations of patients without cancer (3,6,9). The CG formula is known to be markedly less accurate in the elderly and patients with extremes of body composition and decreased muscle mass, scenarios that are common to many patients with cancer (1). However, many oncology clinicians continue to use CG-based eCrCl to guide anticancer drug dosing for kidney function and selection, and some groups and investigators even use multiples of SCr upper limit of normal to determine enrollment into clinical trials. Despite its relative inaccuracy compared with the CKD-EPI equation, the CG formula continues to be the most universally implemented estimator of kidney function in patients with cancer (12,14,19).

Implications for Anticancer Drug Dosing

Many anticancer drugs have a narrow therapeutic index with potentially severe toxicity, and a large number of drugs are excreted predominantly as unchanged drug or active metabolite in the urine and therefore, may require dose adjustment for kidney function (16,17,21). For patients with decreased kidney function, this translates to diminished drug clearance and increased exposure, possibly leading to unacceptable toxicity. Underestimation of kidney function, however, can result in unintentional prescription of a subtherapeutic dose and diminished anticancer activity. Patient-specific dose adjustments of anticancer drugs cleared by the kidneys are, therefore, vital to ensure safety while maintaining anticancer drug efficacy (Table 2). Up to 50% of anticancer drugs either need dose adjustment for kidney function or do not have data on whether dose adjustments are required (2,13,21). Intensive pharmacotherapy and polypharmacy are common features of clinical oncology practice; as such, approximately 50% of kidney function–impaired patients with solid tumors receive at least one anticancer drug that requires dose adjustment for kidney function (2,13,21). However, many patients do not receive appropriate chemotherapy dosage adjustments on the basis of their kidney function. In one retrospective study, approximately one half of kidney function–impaired patients with solid tumors who were receiving a drug that necessitated dose adjustments for kidney function received almost 50% of their prescriptions at standard doses (*i.e.*, without appropriate dose adjustment), potentially causing unacceptable toxicity to the patient. The most commonly implicated drugs included cisplatin, carboplatin, capecitabine, etoposide, and zoledronate. In fact, approximately 3% of patients received a drug for which a dose adjustment would be necessary in the setting of impaired kidney function without receiving any kidney function evaluation (13). This illustrates the lack of a universal approach to evaluating kidney function in patients with cancer and applying the clinical information to tailor pharmacotherapy for individual patients.

Many anticancer drugs are routinely dosed according to BSA in an effort to account for the effect of body size on pharmacokinetics, although this often does nothing to reduce variability in exposure (22). Despite many oncology drugs being dosed according to BSA, the most commonly used method of estimating kidney function in oncology remains the CG formula, which yields an absolute kidney function metric (milliliters per minute) that is not indexed to BSA. This is problematic, because the use of an absolute kidney function estimate to prescribe anticancer drugs that are dosed according to BSA will likely alter the dose assignment compared with dosing decisions on the basis of

Table 2. Selected drugs with kidney function cutoffs for eligibility and dose modifications

Drug	Kidney Function Cutoff Below Which Not to Treat, ml/min	Kidney Function Ranges with Dose Modifications, ml/min	Reference
Bendamustine	30	—	42
Bleomycin	—	5%–10% to 40% 10%–20% to 45% 20%–30% to 55% 30%–40% to 60% 40%–50% to 70%	41
Capecitabine	30	30%–50% to 75%	43
Cisplatin	60	—	37
Etoposide	15	15%–50% to 75%	44
Fludarabine	30	30%–49% to 60% 50%–79% to 80%	45
Methotrexate	60	—	46
Mitomycin	30[a]	—	47
Oxaliplatin	—	<30%–75%	48
Pemetrexed	45	—	49
Pentostatin	—	50%–60% to 50%	50
Topotecan	10	20%–39% to 50%	51

—, not applicable.
[a]Related to hydroxypropyl-β-cyclodextrin excipient.

BSA-indexed kidney function estimates. Small patients will be penalized for having a low absolute kidney function, although their drug dose will already accommodate this size difference (Figure 1). In a *post hoc* analysis of a study using the CG formula (milliliters per minute) to dose stratify patients with impaired kidney function being administered oxaliplatin to develop dosing guidelines, it was revealed that BSA indexing of eCrCl (milliliters per minute per 1.73 m^2) did alter dose classification of several patients versus absolute eCrCl classification. Although this reclassification did not alter the results of the dose guidelines for kidney function determined by the study, it does show that dose stratification of patients can be affected by whether measures of kidney function are indexed for BSA, and this can have potential clinical implications (23,24). The effect of these internal inconsistencies would be most pronounced in the dosing of patient groups with BSAs that differ significantly from 1.73 m^2. Therefore, it would seem pertinent to use BSA-indexed estimates of kidney function for drugs dosed by BSA and absolute estimates of kidney function for drugs dosed absolutely so that the units are congruent (23,25). Notably, the output of the CKD-EPI equation can be easily converted to absolute values through multiplication by (patient's BSA/1.73 m^2).

Case Study: Carboplatin

Carboplatin is a platinum-based alkylating agent that is widely used in the treatment of lung, ovarian, testicular, bladder, breast, and head and neck cancers. Carboplatin exhibits an exposure-response relationship with increasing area under the curve (AUC), resulting in increased antitumor activity; the exposure-response relationship plateaus, and additional increases in exposure result in increased toxicity. An ultrafilterable carboplatin target AUC of 4–6 mg/ml per minute is suggested, because it seems to optimize anticancer efficacy within acceptable toxicities as shown in ovarian cancer (26,27). Even small changes in carboplatin dosing and exposure can have meaningful clinical consequences. For example, a carboplatin dose reduction as small as 10% may result in a doubling of the 5-year relapse rate (28). Currently, carboplatin is dosed on the basis of the Calvert equation (29), with carboplatin dose being directly related to the patient's GFR as follows:

$$\text{Dose(mg)} = \text{target AUC} \times [\text{GFR} + 25].$$

Carboplatin dosing varies significantly depending on the estimate of GFR incorporated into the Calvert formula, and there is poor concordance of carboplatin dose measured with eGFR or eCrCl versus mGFR. Up to three quarters of patients dosed by the CG formula and one quarter of patients dosed by the CKD-EPI equation receive a carboplatin dose over 10% and 20% different, respectively, than the dose that they should receive on the basis of mGFR (12,30). Similarly, only between one fifth and one third of patients prescribed carboplatin have a calculated eGFR or eCrCl within 10% of their mGFR (30). Differences in carboplatin dosing are dependent not only on the method used to calculate GFR (*e.g.*, the CKD-EPI equation versus the CG formula) but also, on whether the BSA-indexed or absolute eGFR is incorporated into the Calvert formula. eGFR indexed for BSA as calculated by the CKD-EPI equation is less likely to overdose but more likely to underdose patients versus absolute eGFR calculated by the same method, further illustrating that the choice of using BSA-indexed versus absolute estimates of kidney function will significantly affect drug dosing and potential clinical efficacy and safety outcomes (Figure 2) (31). Importantly, no studies to date have documented exposure by measuring ultrafilterable carboplatin AUC or examined the differences in clinical safety and toxicity profiles of carboplatin dosing and exposure on the basis of GFR estimation method incorporated into the Calvert formula,

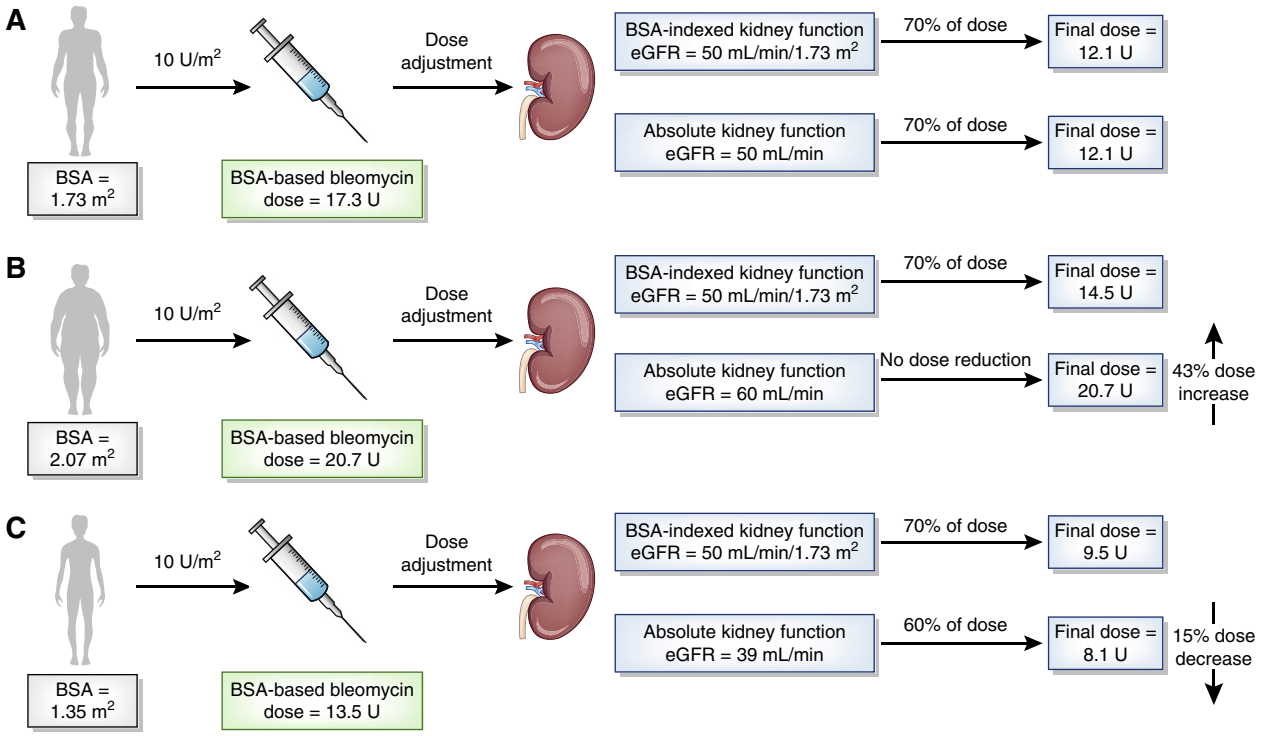

Figure 1. | Many anticancer drugs are dosed according to body surface area (BSA), but they are dose adjusted according to measures of absolute kidney function (*i.e.*, estimated creatinine clearance as milliliters per minute) as opposed to BSA-indexed measures of kidney function (*i.e.*, eGFR as milliliters per minute per 1.73 m^2). (A) This practice will likely alter dose assignments of patients at the extremes of body size (patients who are obese and patients who are cachectic) compared to patients with BSA of 1.73 m^2. (B) Larger patients (BSA>1.73 m^2) are already receiving a larger dose of BSA-dosed drugs due to their increased BSA. Use of an absolute kidney function value may preclude necessary dose reduction, because the absolute kidney function value of patients with BSA>1.73 m^2 will be greater than the BSA-indexed value and may be above a dose-adjustment breakpoint. (C) Smaller patients (BSA<1.73 m^2) are already receiving a smaller dose of BSA-dosed drugs due to their decreased BSA. Use of an absolute kidney function value may lead to additional unnecessary dose reduction, because the absolute kidney function value of patients with BSA<1.73 m^2 will be less than the BSA-indexed value and may be below a dose-adjustment breakpoint. Bleomycin dosing of 10 U/m^2 was on the basis of manufacturer recommendations (41). Absolute eGFR values (milliliters per minute) were calculated by multiplying the BSA-indexed eGFR (milliliters per minute per 1.73 m^2) by (patient's BSA/1.73 m^2).

an effort that is currently being pursued within the Cancer Therapy Evaluation Program of the National Cancer Institute.

Implications for Anticancer Drug Selection

For many anticancer drugs, patients are placed into GFR stratifications, below which administration of the drug is not recommended due to reduced elimination or high potential for toxicity (Table 2). These drugs are generally dosed in a dichotomous fashion as opposed to continuous dosage adjustments, and therefore, accurate determination of patient GFR is critical, because small variations in GFR estimates may completely preclude patients from receiving potentially effective anticancer therapy. This is especially pertinent in stage 2/3 kidney disease, because these stages include the majority of patients with cancer and impaired kidney function and contain important dose adjustment thresholds for many drugs (*e.g.*, 60, 45, and 30 ml/min) (2,13,14,16). Suitability of a drug is most often assessed depending on kidney function as estimated by the CG formula and reported in milliliters per minute; hence, there is considerable ambiguity in assessing drug suitability on the basis of eGFR estimates of kidney function in milliliters per minute per 1.73 m^2. In fact, many studies investigating suitability of cisplatin therapy on the basis of the MDRD equation– or the CKD-EPI equation–derived eGFRs either make no mention of normalizing for patient-specific BSAs but report eGFR in milliliters per minute or use identical numerical cutoffs for both eCrCl (milliliters per minute) and eGFR (milliliters per minute per 1.73 m^2) (32–36). In both the oncopharmacology and clinical oncology communities, more emphasis should be placed on the clinical implications of using BSA-indexed versus absolute estimates of GFR to minimize the likelihood of incorrectly assuming that estimates of kidney function are numerically equivalent across incongruent units.

Case Study: Cisplatin

Cisplatin is a platinum-based alkylating agent that is highly effective at treating many types of cancer. The drug is excreted predominantly unchanged in the urine, and unfortunately, it is extremely nephrotoxic. Although no universal guidelines exist, some recommendations and typical clinical practice discourage use of cisplatin in patients with GFR<60 ml/min (37). In fact, impaired kidney function is the reason for precluding anywhere

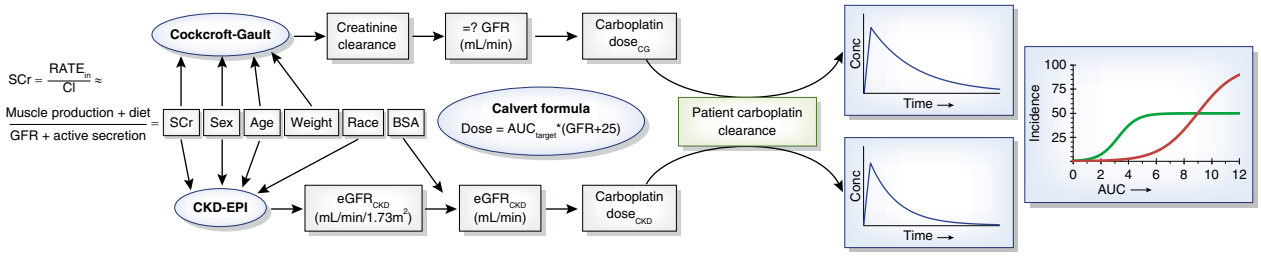

Figure 2. | Area under the curve (AUC)–targeted dosing of carboplatin using either the Cockcroft–Gault formula or the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation to inform kidney function may result in different doses and exposures. The CKD-EPI equation estimates a body surface area (BSA)–normalized GFR value from assumed steady-state serum creatinine (SCr) and anthropomorphic variables. This estimate is converted to an absolute value using the patient's BSA. Similarly, the Cockcroft–Gault formula estimates an absolute value for creatinine clearance, which is then used as a surrogate of GFR. The GFR value is imputed into the Calvert equation with a target AUC (often 6 mg/ml per min), which results in a carboplatin dose to be administered to the patient. On the basis of the true carboplatin clearance of the patient, an exposure is observed. On the basis of a probability of response (green curve) or toxicity (red curve), the exposure and corresponding probability of response and toxicity can be quite different depending on the kidney function estimate used and the corresponding carboplatin dose administered.

from 20% to 83% of patients from receiving cisplatin therapy (32,33,35,36,38).

Cisplatin eligibility varies significantly depending on the kidney function estimate used. For example, CG formula–derived kidney function estimates exclude cisplatin therapy at an approximately 20% higher rate than the CKD-EPI equation–derived estimates (32,33,35,36,38). This bias is especially pronounced in women, the elderly, and whites (32). Patient eligibility on the basis of the CG formula versus eGFR has high discordance, with about 15% of patients changing eligibility status on the basis of the estimation used (32,33,36). Significantly more patients are deemed ineligible for cisplatin with any method of eCrCl or eGFR compared with mCrCl (38). Potentially inappropriate denial of cisplatin eligibility is again seen more prominently in the elderly, with 24%–53% of patients over 65 years old being denied by eCrCl or eGFR but not by mCrCl (34). Notably, the ability of a patient to complete three full cycles of chemotherapy has been correlated with mCrCl>60 ml/min (P=0.02) but not eCrCl>60 ml/min or eGFR>60 ml/min per 1.73 m^2 (34). It is notable that there exists a correlation between a clinical outcome that may directly affect survival and mCrCl, a measured (although admittedly flawed) marker of kidney function, but not eGFR, an estimated and supposedly more accurate measure of kidney function. This calls into question the utility of current drug selection thresholds and their correlation to the various estimates and measures of kidney function in patients with cancer.

Implications for Oncology Clinical Trials

Historically, patients with impaired kidney function have tended to be excluded from phase 1 studies of anticancer drugs because of a perceived increased risk for major dose-limiting toxicity. Recently, however, there has been a call to be more inclusive of patients with mild to moderate kidney impairment in oncology clinical trials (17) as well as warnings to be cautious about sweeping changes (39). Current FDA classification of mild kidney impairment is defined as CrCl=50–79 ml/min, but typical phase 1 eligibility disqualifies patients from enrollment at CrCl<60 ml/min. Therefore, there is a proportion of patients with only mild kidney impairment according to FDA classification who are disqualified from potentially effective clinical trials due to their kidney function. However, a retrospective analysis of over 10,000 patients from 373 single-agent phase 1 clinical trials found that there was no clinically meaningful increase in grade 3 or 4 nonhematologic, grade 4 hematologic, or any clinically relevant toxicities in the approximately 36% of enrolled patients with mild kidney impairment compared with those with normal kidney function (18). Therefore, expanding inclusion of patients to the full FDA classification range of mild impairment (*i.e.*, CrCl>50 ml/min) may increase eligibility of patients without any clinically meaningful difference in determination of the dose-limiting toxicity.

Current FDA guidelines recommend use of the CG formula to determine kidney function (7); however, the draft revision of the guidelines for assessing pharmacokinetics in kidney impairment suggests that the newer eGFR formula also should be used to estimate kidney function (40). Importantly, these draft guidelines do not state a preference as to which formula is used to estimate kidney function, although it is established that the CKD-EPI equation is a more accurate estimate of mGFR across a wider range of kidney function than the CG formula. This is of particular importance in patients with cancer, because at the border of mild to moderate kidney impairment for both FDA classification (50 ml/min) and the majority of phase 1 cancer trials (60 ml/min), the CG formula is known to underestimate kidney function at a higher degree than newer formulas. As such, this may unnecessarily preclude patients with mild kidney impairment from trial participation.

Additionally, there are significant inconsistencies regarding the use of BSA-indexed versus non–BSA-indexed estimates of kidney function to determine dosing and eligibility for anticancer drugs. Recognition of this problem, development of guidelines with the purpose of maintaining consistency in this regard (milliliters per minute for drugs dosed absolutely or on the basis of any non-BSA parameter versus milliliters per minute per 1.73 m^2 for drugs dosed on the basis of BSA), completion of pharmacokinetic trials including patients with impaired

kidney function, and development of corresponding dosing recommendations would significantly improve internal consistency in oncopharmacology.

Summary

Estimation of kidney function in patients with cancer directly affects drug dosing, agent selection, and eligibility for clinical trials of novel agents. It would seem obvious that the most accurate estimates of kidney function should be used to reduce unexplained variability in decision making and ultimately, the therapeutic outcomes of toxicity and clinical benefit. There are many discrepancies between eGFR and true GFR and how these values correlate to absolute and BSA-indexed drug dosing, drug eligibility, and clinical trial enrollment. This illustrates the need for additional studies investigating the validity of currently used estimates of kidney function in patients with cancer, the applicability of traditional anticancer dosing and eligibility guidelines to modern and more accurate estimates of kidney function, and clinical harmonization of kidney function estimation across all patients with cancer.

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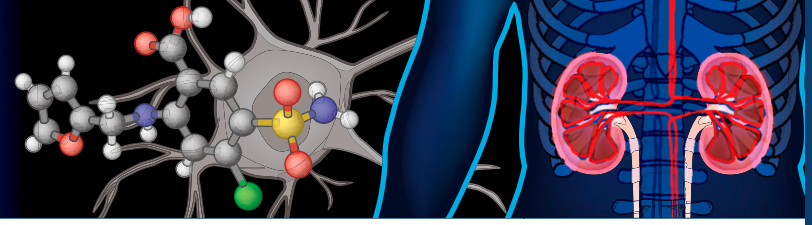

Clinical Pharmacology of Antihypertensive Therapy for the Treatment of Hypertension in CKD

Arjun D. Sinha and Rajiv Agarwal

Abstract

CKD is common and frequently complicated with hypertension both predialysis and in ESKD. As a major modifiable risk factor for cardiovascular disease in this high-risk population, treatment of hypertension in CKD is important. We review the mechanisms and indications for the major classes of antihypertensive drugs, including angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-adrenergic blocking agents, dihydropyridine calcium channel blockers, thiazide diuretics, loop diuretics, mineralocorticoid receptor blockers, direct vasodilators, and centrally acting α-agonists. Recent evidence suggests that β-adrenergic blocking agents may have a greater role in patients on dialysis and that thiazide diuretics may have a greater role in patients with advanced CKD. We conclude with sharing our general prescribing algorithm for both patients with predialysis CKD and patients with ESKD on dialysis.

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Introduction

Treatment of hypertension plays a central role in the management of CKD, including in patients with ESKD. Hypertension is both a cause and a consequence of CKD, and its prevalence is high among patients with CKD and ESKD (1,2). Patients with CKD have an outsized burden of cardiovascular disease; indeed, the presence of CKD represents a coronary risk equivalent on par with diabetes mellitus (3). Additionally, the treatment of hypertension is associated with improved cardiovascular outcomes in both CKD (4) and ESKD (5). Thus, the management of hypertension in CKD and ESKD is both a common and an important issue for patients and practitioners. Nonpharmacologic treatment of hypertension includes dietary sodium restriction (6) and additionally for the dialysis population, vigilant maintenance of an adequate dry weight (7). Despite best efforts, nonpharmacologic methods alone are insufficient in controlling hypertension. In a large CKD cohort, 60% of the patients were being treated with three or more antihypertensive medications, suggesting that resistant hypertension is very common in this population (1).

Given that the pharmacologic treatment of hypertension is an important consideration for the management of CKD, the objective of this review is to survey the clinical pharmacology of the major classes of antihypertensives from a nephrocentric point of view and provide practical insights when using them in patients with CKD and ESKD.

Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers

Angiotensin-converting enzyme inhibitors (ACEis) and angiotensin II receptor blockers (ARBs) are the mainstays of hypertension treatment in CKD. ACEis block the conversion of angiotensin I to the potent vasoconstrictor peptide angiotensin II, whereas ARBs competitively block the angiotensin II receptors (8). This blockade has the effect of reducing aldosterone secretion and reducing peripheral vascular resistance, effectively reducing systemic BP. Importantly, the blockade of angiotensin II also results in dilation of the efferent arteriole of the glomerulus, which reduces intraglomerular pressure and is the putative mechanism for the renoprotective effects of these agents. The use of ACEis and ARBs is now well established for the treatment of proteinuric CKD (9). Heart failure with reduced ejection fraction and acute myocardial infarction (10), both of which commonly coexist with CKD, are other important reasons to treat patients with ACEis or ARBs.

The panel members appointed to the Eighth Joint National Committee (JNC8) found moderately strong evidence to recommend initial or add-on treatment with ACEis or ARBs for hypertension in all patients with CKD to improve kidney outcomes (11). The recently published American Heart Association and American College of Cardiology (AHA/ACC) guidelines on hypertension similarly recommend ACEis or ARBs in CKD stage 3 or higher or those patients with albuminuria of at least 300 mg/d or 300 mg/g creatinine on spot check (12). The broad recommendation of the JNC8 to treat all patients with hypertensive and CKD compared with the more targeted recommendation of the AHA/ACC represents the uncertainty of benefit for ACEi or ARB use in patients with CKD without proteinuria, because the evidence is mixed. Notably, a large

randomized, controlled trial of 1094 subjects found that ramipril use is beneficial to slow decline in GFR, although >65% of subjects in the trial had proteinuria <0.22 on spot ratio (13), whereas a meta-analysis of 11 randomized trials totaling 1860 subjects found no kidney benefit to ACEi use for those subjects with proteinuria <500 mg/d (14). The seeming dilemma is less fraught in practice, however, because patients commonly are not labeled as having CKD unless they have proteinuria or a serum creatinine high enough to merit a diagnosis of CKD stage 3, and furthermore, the majority of such patients with hypertension require multiple agents to achieve adequate control. Furthermore, as noted in the JNC8 recommendations, multiple agents are frequently required to control hypertension in CKD, and therefore, it is reasonable for an ACEi or ARB to be included.

Dual use of ACEi and ARB medications is currently not recommend for treatment of hypertension largely on the basis of the results of the Veterans Affairs Nephropathy in Diabetes Trial in patients with diabetic nephropathy with or without hypertension (15). Subjects were randomized to losartan plus lisinopril versus losartan plus placebo for prevention of a primary composite end point of kidney events or death, and the trial was halted early for lack of efficacy as well as for increased adverse events of hyperkalemia and AKI in the dual therapy group. A *Lancet* meta-analysis notes that the dual renin-angiotensin-aldosterone system blockade may have some benefit (16), but this will require further studies.

Similarly, the direct renin inhibitor aliskiren has antihypertensive efficacy, but its role is undefined: large randomized trials that added aliskiren to ACEi or ARB therapy in diabetes or heart failure found no cardiovascular or kidney benefit, but these trials did show more adverse events for the combinations, including hyperkalemia (17,18). Therefore, direct renin inhibitor drugs plus ACEi or ARB therapy are currently contraindicated. Although there is no evidence for aliskiren being superior to ACEi or ARB therapy to improve clinical end points, the direct renin inhibitor could be used as a substitute renin-angiotensin-aldosterone blocker in the select group of patients who are unable to tolerate ACEi or ARB for reasons other than hyperkalemia.

In the ESKD population, ACEis and ARBs both are effective at lowering BP. Most ACEis are cleared by the kidneys, and it has been shown for both lisinopril (19) and trandolapril (20) that BP is effectively lowered when dosed only three times weekly after hemodialysis (HD), which presents the option of directly observed therapy for hypertension in HD units when medical adherence is a concern; however, because both drugs are dialyzable, the dose should be administered after dialysis. A meta-analysis of three randomized trials using ACEis or ARBs in HD (837 total subjects) found a significant reduction in left ventricular hypertrophy (LVH) but only a trend toward reduction in cardiovascular events (21).

Because the renin-angiotensin-aldosterone system is directly responsible for distal nephron potassium excretion, all blockers of the system promote hyperkalemia, and this is unsurprisingly the common side effect of ACEi and ARB therapy (22,23). When the two classes of drugs are combined, this side effect is even more common. Furthermore, in those with higher baseline potassium and among those with CKD stage 3B or more, the incidence of hyperkalemia is even greater.

β-Blockers

β-Adrenergic blocking agents (BABAs) used to treat hypertension all block the β_1-adrenergic receptors that are expressed primarily in cardiac tissue. Although some BABAs, such as carvedilol and nebivolol, have vasodilating effects, it is the β_1-activity that characterizes the main effects of these medications, with resulting reductions in heart rate and cardiac contractility (8). Although the precise mechanism that leads to long-term reduction in systemic BP remains unclear, a reduction in systemic vascular resistance is thought to mediate the antihypertensive effect of BABAs (24).

There is a large body of evidence showing the benefit of BABAs in the setting of heart failure with reduced ejection fraction (25) and after acute myocardial infarction (26), but despite these benefits, these agents are not recommended for initial monotherapy of hypertension in the general population (27,28). These recommendations from the general population may not apply to patients with CKD. This is because increased sympathetic activity is known to be a contributor to hypertension in CKD, which has been most dramatically shown in ESKD (29). Patients with CKD or ESKD are typically excluded from large trials, and therefore, head to head studies of antihypertensives in CKD or ESKD are few, but a recent randomized, controlled trial in HD comparing lisinopril with atenolol provides some useful observations. The Hypertension in Hemodialysis Patients Treated with Atenolol or Lisinopril (HDPAL) Trial randomized 200 patients on chronic HD with hypertension and LVH to lisinopril- or atenolol-based antihypertensive therapy for 1 year to determine which drug is superior for reduction of LVH (30). All subjects were treated to the same target monthly home BP by first maximizing the study drug and then addition of other drugs, sodium restriction, and reduction in dry weight. The trial was stopped early by an independent data safety monitoring board because of significantly more serious adverse cardiovascular events in the lisinopril group driven by heart failure hospitalizations. LVH improved similarly in both drug groups. The monthly home BP was consistently lower in the atenolol group, despite significantly more antihypertensive medications and nearly 3 kg more dry weight reduction in the lisinopril group (30). Thus, atenolol seems to be superior to lisinopril for BP reduction and possibly, reduction of cardiovascular event rates in this HD population. Additional trials are necessary to confirm the potential superiority of BABAs for reducing cardiovascular events before a broad recommendation can be made. However, in the absence of other head to head trials and on the basis of the results of this single trial, we now routinely start BABAs as the first-line pharmacologic agent for hypertension in our patients on HD. Atenolol, in particular, may be practically useful, because it too can be dosed just three times per week after HD to reduce 44-hour interdialytic ambulatory BP (31), which provides another drug that may be used as directly observed therapy for hypertension in this population. As

with lisinopril, atenolol is also effectively removed by HD and thus, should be dosed after HD.

Because the burden of cardiovascular disease in the predialysis CKD population is high, β-blocker use is common in this population. However, lacking any definitive studies to guide β-blocker prescription in CKD, we do not prescribe these medications as first-line agents for hypertension in this population. However, the surprising findings in the HDPAL Trial raise the question of whether β-blockers may be especially efficacious for managing hypertension and its complications in predialysis CKD, and further study is, therefore, warranted.

BABAs have a host of well described side effects, but bradycardia is the most common concern among patients with CKD and ESKD. Most BABAs are cleared by hepatic metabolism; however, atenolol has only limited hepatic clearance, and drug levels are dependent on kidney elimination, making acute deterioration in kidney function a risk for significant bradycardia. Surprisingly, however, a large retrospective cohort study found that, compared with those on metoprolol, patients prescribed atenolol had reduced mortality and no increased risk of hospitalization for bradycardia or hypotension (32).

In our practice, we avoid prescribing selective α-adrenergic blocking agents, such as doxazosin, for the treatment of hypertension in patients on HD. This is because we have noticed the frequent occurrence of orthostatic hypotension after dialysis, especially among patients who are close to their dry weight. On occasion, these orthostatic symptoms become troubling and have resulted in falls and fractures. Furthermore, although unrelated to CKD, it should be noted that, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial, the α-blocker arm was terminated early due to excess heart failure hospitalization.

Dihydropyridine Calcium Channel Blockers

Calcium channel blockers bind to the α_1-subunit of the L-type calcium channel in muscle cell membranes, reducing calcium flux through the channels and lowering cytosolic calcium concentration, which ultimately reduces muscle contractility (8). The dihydropyridine calcium channel blockers (DHP-CCBs) are so called for their shared chemical structure, and they are more specific for vascular smooth muscle, causing arterial vasodilation with fewer effects on cardiac muscle than the non–DHP-CCBs verapamil and diltiazem. Although non–DHP-CCBs can reduce BP, they are not commonly prescribed in our practice primarily because of many drug interactions, notably with statins and calcineurin inhibitors. Furthermore, non–DHP-CCBs, when combined with BABAs, can provoke atrioventricular conduction delays and complete heart block. The DHP-CCBs are effective and well tolerated, which is why they are recommended first-line therapy in some guidelines for uncomplicated primary hypertension (33). Large trials specifically examining DHP-CCBs for hypertension in CKD are lacking, but these drugs have been used to lower BP as an active comparator in landmark trials of ACEi (13) and ARB (23) agents in CKD. They are effective antihypertensive agents in both CKD and ESKD (34). A major advantage of using DHP-CCBs is that they work well in a volume-expanded state. Furthermore, when used with ACEis or ARBs, they lower BP more than either drug alone.

The DHP-CCBs are highly protein bound and cleared almost exclusively by hepatic metabolism; therefore, their dosing is not affected by kidney dysfunction. The common side effect for these medications is peripheral edema, which improves with cessation of the drug but may also be treated with concomitant diuretic therapy or ultrafiltration on dialysis.

In our approach to prescribing medications for the treatment of hypertension among patients on HD, we use a long-acting DHP-CCB, such as amlodipine or felodipine, as second-line therapy (35). In patients with predialysis CKD, we often prescribe a dihydropyridine as second line to an ACEi or ARB on the basis of their synergistic ability to reduce BP. In patients with contraindications to ACEis or ARBs or cardiac conduction defects, we sometimes use these drugs as first-line agents.

Thiazide Diuretics

Thiazide diuretics are the oldest class of antihypertensive drugs still in use. Thiazides improve cardiovascular outcomes, including stroke, heart failure, coronary events, and death (36,37). The site of action for thiazides is the Na-Cl cotransporter in the distal convoluted tubule of the nephron, which is responsible for around 5% of total sodium reabsorption (8). The first such drugs entered into clinical use in the 1950s and were all derived from benzothiadiazine, leading to the name of the class. Newer diuretics, such as metolazone and chlorthalidone, do not share the same chemical structure, but they share the same pharmacologic mechanism of action and thus, are formerly referred to as thiazide-like diuretics; however, in common practice, all diuretics that act on the Na-Cl cotransporter are called thiazides (Figure 1, Tables 1 and 2).

Thiazide diuretics reduce BP acutely by causing natriuresis, thereby reducing extracellular volume, venous return, and ultimately, cardiac output. However, in the setting of chronic thiazide administration, cardiac output has been shown to return to the pretreatment baseline and total peripheral resistance falls, maintaining the net antihypertensive effect (38,39) The mechanism that causes the fall in total peripheral resistance is unknown but may be related to a slight reduction in volume. In the setting of chronic volume expansion, such as ESKD, an increased cardiac output culminates in increased peripheral resistance and hypertension (40). Notably, natriuresis seems to be essential for BP reduction, because a very high-salt diet at 20 g of NaCl daily for 2 weeks has been shown to reverse the antihypertensive effect of chronic chlorothiazide use (41).

On the basis of very small early studies that predated development and clinical use of loop diuretics, the prevailing dogma has been that thiazides are ineffective at low levels of GFR. Guidelines recommend switching from thiazides to loop diuretics when GFR falls below 30 ml/min per 1.73 m^2 (42). However, the evidence against thiazide use in advanced CKD is weak. The JNC8 and the AHA/ACC recommendations take no position on the use of thiazides versus loop diuretics in CKD (11,12). The Kidney Disease Improving Global Outcomes guidelines are less dogmatic

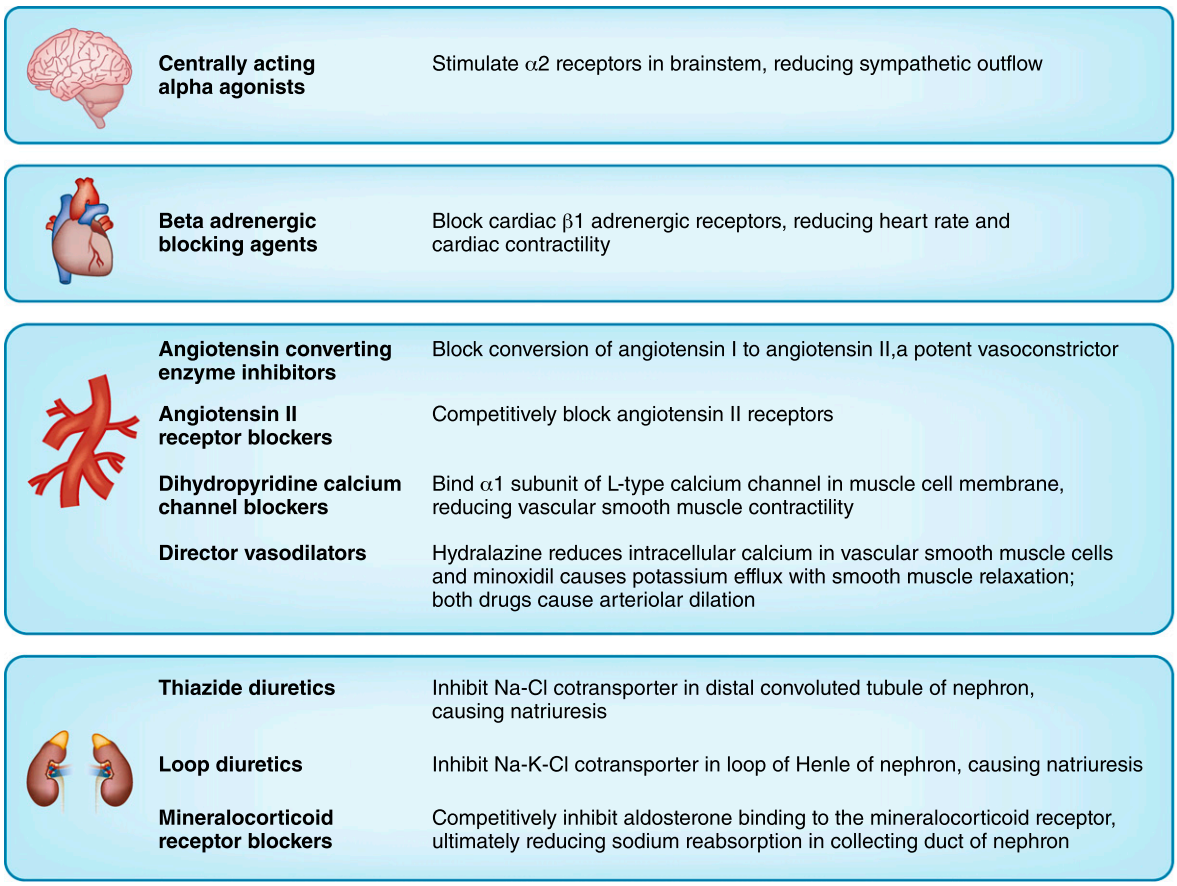

Figure 1. | **Major antihypertensive drug classes and their mechanisms.** Cl, chlorine; K, potassium; Na, sodium.

than before, acknowledging that, although many clinicians switch from thiazides to loop diuretics, the antihypertensive benefit of thiazides may still be preserved at low levels of GFR (43).

In fact, there are ≥14 studies, including five randomized, controlled trials, of thiazides either alone or in combination with a loop diuretic in advanced CKD, and all show some degree of efficacy, whether for hypertension or diuresis (44). Whereas all of these prior studies were small, currently there is an ongoing double-blind, randomized, controlled trial of chlorthalidone in CKD stage 4 for hypertension with a goal of randomizing 160 subjects (45). As with loop diuretics, higher thiazide doses are necessary to achieve a therapeutic effect in the setting of CKD, because these drugs act on the luminal side of the tubular epithelium, and with reduced tubular mass in CKD, less drug is secreted into the tubular lumen (46).

Glucose intolerance and electrolytes abnormalities, including hypokalemia, hyponatremia, and hyperuricemia, are all recognized complications of thiazide therapy and require regular laboratory monitoring when these drugs are used.

There is no role for thiazide diuretics in ESKD, because they are ineffective, and volume removal can be achieved

Table 1. Common adverse effects of the major antihypertensive drug classes in CKD

Drug class	Adverse Effect
ACEIs	Hyperkalemia, cough
ARBs	Hyperkalemia
Dihydropyridine calcium channel blockers	Peripheral edema
Thiazide diuretics	Volume depletion, hypokalemia, hyponatremia, glucose intolerance
Loop diuretics	Volume depletion, hypokalemia
β-Adrenergic blocking agents	Bradycardia, especially with atenolol
Mineralocorticoid receptor blockers	Hyperkalemia, especially when used with ACEi/ARB
Director vasodilators	Peripheral edema, hirsutism with minoxidil
Centrally acting α-agonists	Fatigue, bradycardia especially when used with BABA

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BABA, β-adrenergic blocking agent.

Table 2. Comparison of suggested first-, second-, third-, and fourth-line drug choices for hypertension in predialysis CKD versus ESKD on dialysis

Prescribing Order	Drug Class in CKD	Drug Class in Dialysis	Comments
First	ACEi or ARB	BABA	Atenolol is long acting and effective for hypertension on dialysis
Second	DHP-CCB or diuretic	DHP-CCB	DHP-CCBs are effective and widely available
Third	Diuretic or DHP-CCB	ACEi or ARB	No established role for diuretic in dialysis
Fourth	MRB	Direct vasodilator	Evidence for MRB for resistant hypertension in non-CKD population

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; BABA, β-adrenergic blocking agent; DHP-CCB, dihydropyridine calcium channel blocker; MRB, mineralocorticoid receptor blocker.

with ultrafiltration on dialysis. Furthermore and unsurprisingly, the placebo controlled administration of hydrochlorothiazide 50 mg daily or metolazone 5 mg daily to patients who are anuric on dialysis for 4 weeks showed no improvement in BP (47).

Loop Diuretics

Loop diuretics are so called because their mechanism of action is to inhibit the Na-K-2Cl cotransporter in the apical membrane of kidney tubular epithelial cells located in the thick ascending limb of the loop of Henle, which is responsible for around 25% of sodium reabsorption under normal conditions (8). As a class, loop diuretics are relatively short acting, which has limited their widespread adoption to treat chronic hypertension compared with readily available thiazide diuretics (48). Famously, the trade name for furosemide is Lasix, so called because it lasts only 6 hours. However, as noted above, the tradition has been to change diuretic therapy from thiazides to loop diuretics when GFR declines below 30 ml/min per 1.73 m^2. As with thiazide diuretics, higher doses of loop diuretics will be necessary to achieve a therapeutic effect in CKD (46). Notably, the antihypertensive and diuretic effects of loop and thiazide diuretics are additive (44), which can be vital in the setting of refractory volume overload seen in advanced CKD, congestive heart failure, or end stage liver disease. Similar to thiazide diuretics, volume depletion and electrolyte abnormalities, including hypokalemia, are common complications of loop diuretic therapy, and regular monitoring is, therefore, required.

In the case of ESKD, systematic evidence is lacking, but in practice, loop diuretics are often not discontinued when patients first start dialysis to help address volume overload. As with thiazides, loop diuretics too have been tried in patients who are anuric on dialysis, but doses of furosemide as high as 250 mg intravenously are ineffective (49). Thus, the role for the use of loop diuretics in ESKD is marginal at best, being limited to only those patients with significant residual kidney function. In an effort to minimize polypharmacy in our patients on dialysis, it has been our practice to discontinue diuretics in our patients when they initiate kidney replacement therapy.

Mineralocorticoid Receptor Blockers

Under normal conditions, aldosterone enters the kidney collecting duct cells *via* the basolateral membrane and binds with the mineralocorticoid receptor in the cytosol before translocating to the nucleus, where the aldosterone receptor complex regulates gene expression, including a cascade of steps that prevent the turnover and degradation of epithelial sodium channels on the apical side of the collecting duct cell (8). Mineralocorticoid receptor blockers (MRBs) competitively inhibit aldosterone binding to the mineralocorticoid receptor, which ultimately increases epithelial sodium channel degradation and thus, results in reduced sodium reabsorption at the expense of reduced potassium excretion.

The available mineralocorticoid receptor antagonists spironolactone and eplerenone have well established roles in the general population with heart failure (50,51) and recognized efficacy for treating resistant hypertension (52). In the setting of CKD, there is also growing interest in using spironolactone to reduce proteinuria as shown in a recent meta-analysis that included studies of MRBs added to ACEis or ARBs in the setting of CKD; it found that MRB use was associated with both reduced BP by 6 mm Hg systolic and proteinuria reduced by 40% (53). Hard cardiovascular or kidney end points could not be assessed by the meta-analysis, but the findings are encouraging, and we await appropriately designed randomized trials to explore this promise further.

Both spironolactone and eplerenone are hepatically metabolized. In the case of the eplerenone, the metabolites are inactive, but with spironolactone, many metabolites are active and excreted by the kidney; thus, extra caution must be taken in the setting of CKD. As with ACEis and ARBs, hyperkalemia is the major limiting side effect, precluding the widespread use of MRBs. In our clinical practice, we have adopted an aggressive approach to prescribing MRBs in CKD, especially in patients who are hypokalemic because of ongoing therapy with thiazide or loop diuretics.

In ESKD, spironolactone has been shown to significantly improve 24-hour ambulatory BP (54), but most impressively, two randomized, controlled trials of spironolactone on dialysis have shown reduced cardiovascular mortality (55,56). Notably, hyperkalemia was only a rare complication in these trials of patients on dialysis. It is likely that the salutary effects of spironolactone are due to mechanisms other than alteration of kidney sodium and potassium handling, because an explicit inclusion criterion for one trial was for oliguria. Therefore, the beneficial effects of spironolactone are plausibly due to a direct cardiac or vascular mechanism. Several follow-up studies are ongoing, and results must be analyzed

before widespread use of MRBs in dialysis can be recommended; however, we have been more liberal in prescribing spironolactone to our patients who are hypertensive with ESKD who only rarely miss HD.

Direct Vasodilators

The oral direct vasodilators are hydralazine and minoxidil. Hydralazine's precise mechanism is unclear, but it culminates in a fall in intracellular calcium in vascular smooth muscle cells (8). Minoxidil is hepatically metabolized to its active metabolite, which inhibits the ATP-modulated potassium channels of vascular smooth muscle, leading to potassium efflux and smooth muscle relaxation (8). Hydralazine and minoxidil are similar in that both cause arteriolar dilation without venous dilation and both cause reflex tachycardia and volume retention with edema, which can manifest as pericardial effusion in extreme cases. Minoxidil uniquely also reliably causes hirsutism in a dose-dependent fashion. Hydralazine is rapidly metabolized by the liver to inactive metabolites, whereas minoxidil is also primarily hepatically metabolized; however, roughly 20% is excreted in the urine as unchanged drug, which may explain why it can be effective when dosed only once daily in CKD.

Both vasodilator agents can lower BP in CKD or ESKD, but they are typically reserved as last-line therapy for hypertension due to lack of proven efficacy for reducing clinically relevant outcomes. The exception is that hydralazine is being used more often on the basis of results of the African American Heart Failure Trial that showed evidence of mortality benefit in combination with isosorbide dinitrate (57), but it is important to recognize that subjects with significant kidney disease were excluded from the trial and that the combination of medications has not been studied specifically in CKD or ESKD. Furthermore, the pill burden and requirement of three to four times daily dosing of hydralazine make its use less attractive. It is for that reason that we recommend minoxidil over hydralazine on account of its long duration of action, providing antihypertensive effectiveness with only once daily dosing in the setting of CKD.

Centrally Acting α-Agonists

The centrally acting α-agonists clonidine and guanfacine are so called because their mechanism of action is to stimulate α_2-receptors in the brainstem, reducing sympathetic outflow (8). Both medications frequently cause dry mouth, sedation, and bradycardia, and both drugs exhibit rebound hypertension when stopped abruptly. Both medications are 50% excreted as unchanged drug in the urine, which therefore, requires greater vigilance for side effects when used in patients with CKD. Although this class of medication can treat hypertension in both CKD and ESKD, on account of their side effects, they are typically reserved only for those patients whose BP is uncontrolled on numerous other medications. To minimize pill burden and dosing schedule, we prefer to avoid oral clonidine and instead use the long-acting clonidine patch, which can be administered once a week at the dialysis unit as directly observed therapy. Because the clonidine patch can be expensive, a cheaper alternative is oral guanfacine, which is longer acting and thus, can be dosed only once daily at bedtime to minimize the dose-related drowsiness.

Suggested Initial Prescribing Algorithm

In the setting of predialysis CKD and in the absence of specific indications for other drugs, our practice is to prescribe an ACEi or ARB as first-line therapy for hypertension in accordance with the recent AHA/ACA recommendations for patients with CKD stage 3 or greater or those with albuminuria of at least 300 mg/d or 300 mg/g creatinine on spot check, which describes the vast majority of patients who we see (12). In our hands, second-line therapy is between a DHP-CCB or a diuretic, with the latter chosen if the patient has signs of volume overload or if we judge that an MRB will be urgently necessary to manage uncontrolled proteinuria and wish to lower potassium before starting the MRB. When using diuretics, we typically choose chlorthalidone or torsemide due to their long durations of action. We prefer chlorthalidone over hydrochlorothiazide because of its longer duration of action and greater potency. We prefer chlorthalidone over metolazone because of its lower cost. Our choice for third-line therapy completes the triad of ACEi or ARB, DHP-CCB, and diuretic. Those patients with uncontrolled hypertension despite adequate doses of those three agents have resistant hypertension by definition, and we routinely prescribe spironolactone as a fourth agent in this scenario on the strength of the PATHWAY-2 Trial (52), which showed efficacy for spironolactone to reduce home BP in subjects with resistant hypertension despite ACEi, DHP-CCB, and thiazide diuretic use. Importantly, this is an extrapolation to the CKD population, because the PATHWAY-2 Trial excluded subjects with CKD stage 3B or worse, and the average eGFR was 91 ml/min per 1.73 m^2 for trial subjects.

Notably, with the availability of new oral potassium exchange compounds patiromer and potentially, zirconium cyclosilicate, there is renewed interest in using these drugs to prevent hyperkalemia and permit prescription of ACEi, ARB, and MRB drugs in the setting of CKD. In contrast, we are of the opinion that aggressive use of inexpensive thiazide-like and loop diuretics alone or in combination can often control and prevent hyperkalemia and may preclude the need of more expensive, newer potassium exchange drugs. We acknowledge that definitive trials comparing the two approaches are lacking.

When resorting to pharmacotherapy for hypertension on HD, in the absence of specific indications for other drugs, we prescribe atenolol as first-line therapy on the basis of the results of the HDPAL Trial (30). For second-line therapy, we use dihydropyridines. We use ACEis or ARBs as our third-line choice. Although the early studies suggesting that MRBs reduce cardiovascular mortality in ESKD are promising (55,56), because of the risk of hyperkalemia, we do not prescribe MRBs routinely and await larger and more definitive studies.

Disclosures

Dr. Sinha had consulted for Janssen and received research funding from Bayer. Dr. Agarwal has consulted for the following companies:

Akebia; Astra Zeneca; Bayer; Boehringer Ingelheim; Celgene; Daiichi Sankyo, Inc.; Eli Lilly; Glaxo Smith Kline; Ironwood Pharmaceuticals; Janssen; Reata; Relypsa; Sanofi and Genzyme US Companies; Takeda Pharmaceuticals, USA; and ZS Pharma.

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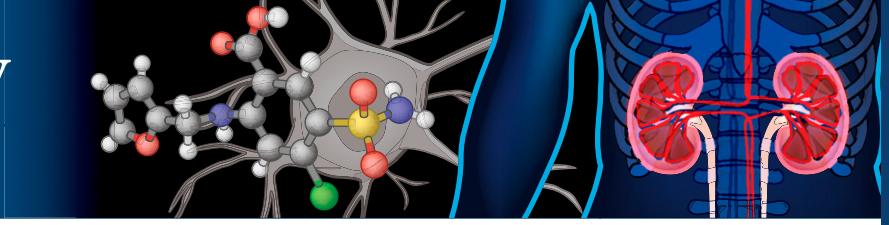

Clinical Pharmacology Considerations in Pain Management in Patients with Advanced Kidney Failure

Sara N. Davison

Abstract

Pain is common and poorly managed in patients with advanced CKD, likely due to both under and over prescription of appropriate analgesics. Poorly managed pain contributes to patients' poor quality of life and excessive health care use. There is tremendous variability within and between countries in prescribing patterns of analgesics, suggesting that factors other than patient characteristics account for these differences. This article discusses the pharmacologic management of acute and chronic pain in patients with advanced CKD, and the role analgesics, including opioids, play in the overall approach to pain management.

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Introduction

Pain is common in patients with advanced CKD. Over 58% of patients experience pain and approximately 49% of patients report moderate or severe pain, whether they are treated with dialysis or managed conservatively (1). It is widely recognized that pain, in particular chronic pain, is associated with psychologic distress; depressive disorders; limitations in work, family, and social life; decreased life satisfaction and quality of life (QOL); and increased hospitalizations and emergency department visits (2–5). For patients receiving hemodialysis (HD), uncontrolled pain leads to shortened or missed treatments (6). Chronic pain in the United States costs hundreds of billions of dollars annually (7).

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" (8). This definition recognizes pain as a multidimensional phenomenon with physical and psychosocial components. A unidimensional approach to pain management, especially one that relies exclusively on analgesics, is unlikely to be successful. Nonpharmacologic therapies that address the whole person in the context of their disease and personal life are vital in managing chronic pain and should augment pharmacologic treatments (*i.e.*, multimodal therapy). These may include physical therapies such as aerobic exercise, stretching, massage, acupressure, and acupuncture; behavioral therapies such as cognitive behavioral therapy, biofeedback, relaxation techniques, counseling, guided imagery, and mindfulness-based stress reduction; as well as interventions such as nerve blocks and trigger point injections.

The focus of this article is the pharmacologic management of acute and chronic pain in patients with advanced CKD, including patients with ESKD treated with dialysis or conservative kidney management. The role analgesics play in the overall approach to pain management will be discussed, with the understanding that analgesics should not be the sole focus of treatment and should only be used when needed, in conjunction with other treatment modalities, to meet patient-specific treatment goals.

Key Considerations in the Evaluation of Pain to Guide Pharmacologic Management

Evaluation of pain requires a comprehensive patient assessment and physical examination that includes understanding the patient's diagnosis and medical history in addition to determining the effects of the pain on the patient's psychologic status, social functioning, functional status, and QOL. Four aspects of the evaluation essential to determining a pharmacologic approach will be discussed here. They consist of determining (*1*) pain intensity; (*2*) chronicity and possible reversible causes for the pain; (*3*) the type of pain—nociceptive, neuropathic, or combined; and (*4*) treatment goals.

Pain Intensity

Determining pain intensity helps establish the need for treatment. The experience of pain is unique to each individual and can only be measured by that individual. Listening to the patient validates the significance of their pain and their suffering and is an important part of the therapeutic intervention. Several global symptom assessment tools have been validated for use in patients with CKD. These have recently been reviewed elsewhere (1). These tools differ in format, such as numeric, visual, or verbal scales. Although each has evidence for validity, patients interpret them differently, making it difficult to compare between studies. Substantial data exist

around what constitutes clinically significant pain. Most of these data are on the basis of 0–10 scales and consensus from the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials was to recommend using a 0–10 numeric rating scale, at least in pain studies (9). This also helps compare findings across patient populations and studies. A score of 0–3 generally reflects mild pain, which does not usually require initiation of or change in pain management. Moderate pain with a score of 4–6 generally means therapy has to be initiated or changed because pain is managed inadequately. A score of 7–10 is described as severe pain and typically requires immediate attention to treatment.

The Edmonton Symptom Assessment System–revised: Renal is a quick, simple, and widely used global symptom assessment tool that can be used successfully in patients, even as they approach death (2). The most recent version consists of a 0–10 numeric rating scale for 12 commonly experienced symptoms, including pain (10).

Chronicity of Pain and Reversible Factors

Determining the chronicity of pain is important in determining appropriate management strategies (Table 1). With acute pain it is important to treat underlying causes to ensure long-term resolution. One should initiate analgesics promptly with moderate or severe pain because pain is more difficult to treat once the pain cycle becomes established. Although we still do not fully understand the development of chronic pain, lessons learned from patients undergoing surgery have taught us that good pain control reduces the likelihood of experiencing chronic pain after surgery. We also know that the risk of abuse is low in patients receiving opioids for acute pain after surgery if the opioids are used in a controlled manner.

Patients with chronic pain often do not have a treatable underlying cause for their pain and the somatosensory component of the pain assumes greater prominence than in acute (and, some say, cancer) pain. As the disorder progresses, the original triggers become less important and psychologic mechanisms gain importance. Pharmacologic therapy alone is unlikely to be sufficient and pain scores have not been shown to correlate with analgesic therapy, including opioid use. For patients with chronic pain, nonpharmacologic assessment and support is essential. The management of recurrent pain, such as pain from needling fistulas, intradialytic steal syndrome, intradialytic headaches, and cramps (Table 1), is more in keeping with acute pain. It focuses on strategies to minimize tissue

Table 1. Chronicity and type of pain

Pain	Details
Chronicity of pain	
Acute pain	• Typically persists for <3 mo. • Associated with tissue damage. • Usually episodic with periods without pain. • Tends to last a predictable period, have no progressive pattern and subsides as healing occurs. • Tends to respond well to pharmacologic therapy: titrating analgesics against pain intensity usually works well.
Chronic pain	• Often defined as any painful condition that persists for >3 mo (8). • Usually initiated by tissue injury but is perpetuated by neurophysiologic changes, which take place within the peripheral and central nervous system leading to continuation of pain once healing has occurred. • Severity is often out of proportion with the extent of the originating injury. • More likely to result in functional impairment and disability, psychologic distress, sleep deprivation, and poor QOL than acute pain. • The pain experience may be affected substantially by mood, stress, and social circumstances. • May not respond well to analgesics, including opioids, except early in the course of treatment.
Recurrent pain	• Acute pain from tissue injury, which may occur over long periods of time (*e.g.*, pain from needling fistulas, intradialytic steal syndrome, intradialytic headaches, and cramps). • Patient will also be free from pain for long periods. • More intrusive on everyday life than "acute pain."
Type of pain	
Nociceptive pain	• Results from tissue damage in the skin, muscle, and other tissues, causing stimulation of sensory receptors. • May be described as sharp or like a knife and often felt at the site of damage (*e.g.*, joint pain from dialysis-related arthropathy). • With stimulation of visceral nociceptors, may be experienced as dull, aching, and poorly localized (*e.g.*, gut ischemia). • Tends to respond to analgesics.
Neuropathic pain	• Results from damage to the nervous system resulting in either dysfunction or pathologic change. • May be felt at a site distant from its cause (*e.g.*, in the distribution of a nerve). • Common descriptors include burning, shooting, and electrical. • May be associated with episodes of spontaneous pain, hyperalgesia, and allodynia; the presence of allodynia is pathognomonic. • Examples include peripheral neuropathy. Severe pain associated with limb ischemia and calciphylaxis tend to have substantial neuropathic components. • Responds poorly to analgesics and typically requires adjuvant therapy such as anticonvulsants (gabapentinoids or carbamazepine) and tricyclic antidepressants.

QOL, quality of life.

injury and short-term pharmacologic management around the time of tissue injury if the cause cannot be avoided.

Type of Pain

The choice of initial analgesic is dependent upon the type of pain. In particular, neuropathic pain should be distinguished from nociceptive pain (Table 1). Neuropathic pain is poorly responsive to nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids or requires doses for response that are associated with unacceptable toxicity. The initial treatment of neuropathic pain is an adjuvant drug, which is a drug that has a primary indication other than pain. In contrast, nociceptive pain responds well to nonopioid and opioid analgesics, at least in the short term. Many pains experienced by patients with CKD will be of mixed type, *e.g.*, pain associated with ischemia and calciphylaxis. It is important to target the neuropathic component first with adjuvant therapy to prevent inappropriate use of opioids.

Elucidating these three components of the pain assessment (intensity, chronicity, and type of pain) can be done through the "PQRST" approach: Provokes and Palliates, Quality, Region and Radiation, Severity, and Time, as outlined in Table 2 (11).

Treatment Goals

Developing a treatment plan includes explaining the nature of the pain condition and setting appropriate treatment goals. Because relief of all pain is generally not possible, especially with chronic pain, the goal of therapy is to relive the pain to a tolerable level, allowing for acceptable function and QOL. For most patients this is a target of ≤3 out of 10. It is important that the clinician be honest and establish realistic expectations. Management may need to be staged, initially aiming for freedom from pain at rest and at night, progressing to relief of more difficult pain such as that which is related to specific activities such as walking.

Current Status of Analgesic Use among Patients with Advanced CKD

The World Health Organization (WHO) analgesic ladder has been advocated for the management of pain, including chronic pain in patients with CKD (12). A short, 4-week study of 45 patients receiving HD with mild or moderate pain showed a substantial reduction in mean pain scores for both nociceptive and neuropathic pain by using the WHO analgesic ladder approach to management (13).

Table 2. The "PQRST" approach to evaluating pain (11)

Components of the Assessment	Questions to Explore
P=Provokes and palliates	What causes the pain? What makes the pain better or worse?
Q=Quality	What does the pain feel like? Is it sharp? Dull? Stabbing? Burning? Crushing?
R=Region and radiation	Where is the pain located? Is it confined to one place? Does the pain radiate? If so, where to?
S=Severity	How severe is the pain?
T=Time (or Temporal)	When did the pain start? Is it present all of the time? Are you pain-free at night or during the day? Are you pain-free on movement?

The WHO analgesic ladder was introduced initially for terminally ill cancer patients who were dying in pain. It involves the slow introduction and upward titration of analgesics, starting with nonopioids then progressing to weak then strong opioids as required for pain relief. The success of this approach led to the expansion to patients with chronic nonmalignant pain and an unprecedented increase in the prescribing and dose of opioids. Nowhere has this been more pronounced than in the United States, and it has been associated with an increase in opioid-related deaths; higher rates of addiction and social dysfunction; cognitive impairment; falls and orthopedic injuries in the elderly; and an increase in emergency department visits and in-patient hospitalizations (14,15) without clear evidence that treatment relieves chronic pain in the long term. The rates of harm correlate directly with dose, which in turn is associated with continuous use.

The substantial harms associated with opioid misuse have been reported at the population level. Those at increased risk are adults aged 18–25 years, decreasing with increasing age (although death rates from opioid overdoses are highest in 45–54-year-olds); men; those with lower educational attainment; and people with psychiatric conditions or a history of substance or sexual abuse (14,15). It is unclear how the legitimate concerns of opioid misuse pertain to patients with advanced CKD. These patients have serious chronic illness with comorbidities such as bone disease, diabetes, and peripheral vascular disease, all of which are known to be associated with ongoing tissue injury and painful conditions. Are these patients more like those with terminal cancer and could they benefit from chronic (low dose) opioid use? The answers are unknown because we lack quality evidence to optimize safe and effective management. However, current prescribing of opioids for patients on HD, at least in the United States, is associated with significantly higher risk of altered mental status, falls, or fractures in a dose-dependent manner (16).

The current situation of poorly managed pain is likely due to both under and over prescription of appropriate analgesics for patients with advanced CKD (17). The prevalence of overall analgesic and opioid use in CKD is highly variable across studies. A recent meta-analysis reports an estimated prevalence of overall analgesic use in patients with advanced CKD of 47% (95% confidence interval (95% CI), 0.35 to 0.59), opioid prevalence 22% (95% CI, 0.07 to 0.41), acetaminophen prevalence 26% (95% CI, 0.16 to 0.36), and NSAID prevalence 16% (95% CI, 0.11 to 0.21) (S.N. Davison *et al.*, submitted article). The prevalence of opioid use is much higher in the United States compared with European countries, Canada, Australia, and New Zealand. A recent, large study across the United States showed that 64% of 153,758 patients on dialysis in 2010 received opioids: 41% of patients had a short-term prescription, whereas 23% received a chronic opioid prescription defined as ≥90 days (18). Chronic opioid prescription rates ranged from 9.5% of patients on

dialysis in Hawaii to 40.6% of patients in West Virginia. Eight states had prescription rates >30%. Such high variability suggests that factors other than patient characteristics account for prescribing differences. Equally concerning was the choice of opioid used: 10.6% of patients received chronic prescriptions for opioids that are not recommended, including 1.4% of patients using propoxyphene, an opioid that has been withdrawn from the market across Europe, New Zealand, and Canada. The US Food and Drug Administration advisory panel also recommended against the use of propoxyphene, after concluding that the safety risks outweighed its limited benefit. However, the end result was a black box warning only. In addition, 11.7% of patients were prescribed hydrocodone chronically, an opioid for which there is no evidence of its safety in CKD. Only 1.9% of patients received a chronic prescription for an opioid that is currently considered safer and therefore recommended for use in these patients.

The Five Essential Principles for the Pharmacologic Management of Pain

The essential principles of pain management are summarized by five phrases that are described within the context of advanced CKD in Table 3. Of particular importance is the careful selection of analgesics. Current recommendations are based primarily on indirect pharmacologic evidence and clinical experience, *i.e.*, "expert advice," rather than quality clinical studies. On the basis of our current understanding, the analgesics that should be avoided in patients with advanced CKD and the evidence behind the recommendations are outlined in Table 4.

Nonopioids in Advanced CKD

Acetaminophen

Acetaminophen is an antipyretic analgesic with weak anti-inflammatory activity. In therapeutic doses it has no other important pharmacologic effects. It is metabolized extensively in the liver. Only 2%–5% of the dose is excreted unchanged in the urine and there are no clinically significant changes observed in patients with kidney failure. Recent evidence suggests that lifetime cumulative doses of acetaminophen do not have an adverse effect on CKD progression rate (19). Liver injury can be seen with acetaminophen doses of <4000 mg; therefore, the recommended maximum daily dose is 3000 mg.

NSAIDs

The American Geriatric Society recommends that the chronic use of all oral NSAIDs, including high-dose aspirin, be avoided, especially in the elderly >75 years

Table 3. The five principles of pain management within the context of advanced CKD

Principle	Description	Specific Considerations in Advanced CKD
"By mouth"	• Oral administration is the safest and therefore usually preferred. • If ingestion or absorption is uncertain, analgesics need to be given by alternative routes such transdermal, rectal, or subcutaneous.	• Patients on HD have easy intravenous access. However, this is to be avoided as the route of administration for analgesics to optimize safety and minimize the risk of abuse and addiction.
"By the clock"	• For continuous or predictable pain, analgesics should be given regularly. Additional "breakthrough" or "rescue" medication should be available on an "as needed" basis in addition to the regular dose.	• Some patients with mild-to-moderate pain may achieve adequate pain relief with analgesic dosing post-HD only. An example would be mild-to-moderate neuropathic pain dosed with gabapentin postdialysis.
"By the ladder"	• Pharmacologic management proceeds stepwise from nonopioids to low-dose opioids. • The drug should be used at its full tolerated dose before moving to the next level.	• Careful selection of analgesics with gradual titration is essential (Figure 3). • Sustained-release preparations are generally not recommended, at least until the individual patient's response to the medication has been observed, due to the narrow therapeutic window in patients with advanced CKD. There is also some evidence for increased mortality with long-acting opioids (34).
"For the individual"	• The "correct" dose for strong opioids is the amount needed to relieve the pain without producing intolerable side effects. Evaluation of benefit and toxicity is essential. • If an individual finds that a particular strong opioid causes unacceptable adverse effects, an alternative must be sought.	• Chronic pain is often experienced in the context of numerous other physical, psychosocial, and spiritual concerns, including end-of-life issues. Close attention to these other issues must not be forgotten if the pain management strategy is to be successful.
"Attention to detail"	• Pain changes over time; therefore, there is the need for ongoing reassessment. • Side effects of opioids should be explained and managed actively; *e.g.*, constipation and nausea with anticipatory prescribing of a bowel routine (*e.g.*, PEG 3350) and antiemetic (*e.g.*, Zofran 4–8 mg).	• There are no studies on the long-term use of analgesics in patients with CKD. Careful attention must be paid to efficacy and safety. • The effect on overall symptom burden, physical function, emotional state, cognition, and QOL should be assessed routinely.

HD, hemodialysis; QOL, quality of life.

Table 4. Analgesics to avoid in patients with advanced CKD

Analgesic	Details
NSAIDS (for chronic pain) (20)	The major limitation is gastrointestinal toxicity due to inhibition of cytoprotective mucus secretion and impaired platelet aggregation resulting in ulceration and bleeding. Risk increases in severity and frequency with increasing age: NSAID use increases the risk of gastrointestinal bleeding in the elderly four-fold. Concomitant use of antiplatelet drugs such as aspirin, anticoagulants, and SSRIs further increases bleeding risk. Although the gastrointestinal safety profile of COX-2 inhibitors is superior to nonselective NSAIDs, nephrotoxic and cardiovascular adverse effects (myocardial infarction, thrombotic events, and stroke) remain significant. It has been shown that the long-term use of all NSAIDs increases the risk of stroke by 64% at 2 yr. COX-2 selectivity may not play a role in the increased cardiovascular risk of NSAIDs because rofecoxib was the only drug in meta-analyses to demonstrate excessive harm and skewed the data of COX-2 selective NSAIDs (35). There is insufficient evidence to confirm any NSAID to be safe in terms of cardiovascular risk. In patients with residual kidney function, NSAIDs may also cause: a reduction in GFR that can be severe and irreversible if the patient has decreased effective circulating volume; sodium and water retention, which may aggravate hypertension and hyperkalemia. The elderly may be at increased risk for NSAIDs-associated psychiatric events such as agitation, depression, anxiety, paranoia, delirium, and hallucinations.
Codeine	A weak opioid that is metabolized by the enzyme CYP2D6 in the liver to its active metabolite morphine, which provides the analgesic effect. Only about 5%–10% of codeine is metabolized in this pathway, with most of the administered dose being converted to inactive metabolites. The percentage of codeine converted to morphine can be much higher in individuals who have three or more active copies of the *CYP2D6* gene ("ultra-rapid metabolizers"), resulting in life-threatening or fatal respiratory depression due to high plasma levels of morphine, even with trivial doses. Conversely, poor analgesic response will be seen in those who carry inactive copies of *CYP2D6* ("poor metabolizers") due to low morphine levels after administration of standard doses (25). Up to 11% of codeine is also metabolized to hydrocodone (mechanism unknown). Both codeine and its metabolites are excreted by the kidneys and accumulate in patients with kidney failure.
Dextropropoxyphene	A weak opioid that has been withdrawn from the market in the United Kingdom, Europe, New Zealand, and Canada due to its weak analgesic effect, addictiveness, and its association with deaths and possible arrhythmias. In the United States it has a Black Box warning and is on the High-Risk Medications in the Elderly list. Decreased elimination of dextropropoxyphene and its major active metabolite, norpropoxyphene, occurs in patients with kidney failure (36).
Tramadol	A weak synthetic opioid related to codeine. Extensively metabolized in the liver with one main active metabolite, M1. Both the parent drug and M1 contribute to the analgesic effect through u-opioid receptors and two nonopioid mechanisms, inhibition of serotonin and norepinephrine reuptake (37). M1 has a significantly higher affinity for opioid receptors than tramadol, whereas tramadol is a more potent inhibitor of serotonin and norepinephrine reuptake (38). The enzyme CYP2D6 catalyzes the production of M1 and other CYP enzymes (CYP2B6 and CYP3A4) catalyze the production of M2, an inactive metabolite (Figure 1). Unpredictable risk of serious overdosing or under dosing after administration of standard doses. The concentrations of tramadol may be 20% higher in "poor metabolizers" versus individuals who have multiple functional copies of the CYP2D6 gene ("ultra-rapid metabolizers"), whereas M1 concentrations may be up to 40% lower. Factors such as the concurrent use of CYP2D6 inhibitors (Figure 2) could also result in increased tramadol concentration and decreased M1 concentration. Induction of CYP3A4 may pose an added risk of seizures, even when tramadol is administered in accepted doses. This is particularly problematic in the context of neuropathic pain where several of the adjuvants are CYP3A4 inducers (Figure 2). Serotonin syndrome is a potentially life-threatening syndrome that may occur with the use of tramadol, especially if other medications such as antidepressants or other drugs that impair the metabolism of tramadol (CYP2D6 and CYP3A4 inhibitors) are used concurrently. Symptoms include changes in mental status (*e.g.*, agitation, hallucinations, coma), autonomic instability (*e.g.*, tachycardia, labile BP, hyperthermia), neuromuscular aberrations (*e.g.*, hyperreflexia, incoordination), and/or gastrointestinal symptoms (*e.g.*, nausea, vomiting, diarrhea).
Morphine	Metabolized primarily to the active metabolite M3G and small amounts (approximately 10%) of M6G. M3G lacks analgesic effect but may have neuroexcitatory effects contributing to adverse effects such as allodynia, myoclonus, and seizures. M6G has potent analgesic effect, more so than morphine. Although M6G is dialyzed, it diffuses out of the central nervous system slowly so may not be completely removed during dialysis. M3G and M6G (more so than the parent drug morphine) accumulate in patients with advanced CKD. There is poor, inconsistent correlation between plasma levels of morphine, M3G, and M6G and clinical efficacy or adverse effects (39). The best correlation appears to be between higher levels of morphine and constipation and high levels of M3G and cognitive impairment (26). There are many reports in the literature of profound toxicity in patients with advanced CKD.

Table 4. (Continued)

Analgesic	Details
Oxycodone	A semisynthetic opioid metabolized primarily by CYP3A4 to the active metabolite noroxyodone with a small amount metabolized by CYP2D6 to the active metabolite oxymorphone, the clinical relevance of which is not clear. The potential for drug interaction and unpredictable pharmacodynamic response therefore is relatively high (Figure 1). Less than 10% is excreted unchanged in the urine. Despite this, both the parent drug and the active metabolites appear to accumulate in patients on dialysis (40) with reports of toxicity (41). The central opioid effects are governed by the parent drug. A recent systematic review of opioid use in patients with cancer with some degree of kidney failure found two studies that evaluated oxycodone use: higher oxycodone levels were associated with increased fatigue but the metabolite noroxycodone was not associated with any of the evaluated adverse effects (26). A single study assessed the pharmacokinetics after a single 20-mg oral dose of an abuse-deterrent formulation of extended release oxycodone in patients with mild ($n=6$), moderate ($n=5$), and severe ($n=6$) kidney failure (42). Cmax and AUC continued to increase with increasing severity of kidney failure and patients with severe kidney failure had a Cmax (31.6 ng/ml versus 17.6 ng/ml) and AUC (493.5 ng.h/ml versus 210.7 ng.h/ml) more than double that of those with normal kidney function. Adverse effects were experienced by 50% of patients with severe kidney failure versus 14.3% in those with normal kidney function. In a case study of a single patient on HD, oxycodone and its metabolites were reduced by dialysis, yet there was no loss of analgesia (43). More recently, knowledge about the dialyzability of oxycodone comes from a study of 20 patients on HD on stable doses of oxycodone CR (44). Dialyzability of oxycodone and noroxycodone was possible but very limited. Not surprisingly, therefore, there was no significant increase in postdialysis pain with no need for additional opioid dosing. This is not surprising because oxycodone has a relatively high volume of distribution (greater than hydromorphone), is nearly 50% protein bound, and is only moderately water soluble.
Hydrocodone	A semisynthetic strong opioid synthesized from codeine: 99% of the world's supply is consumed in the United States where it is the most commonly prescribed opioid, including for patients with CKD. Primarily metabolized in the liver into several metabolites, including hydromorphone, *via* CYP2D6. Therefore, it might be expected to have a similar unpredictable risk of serious overdosing or under dosing after administration of standard doses as seen with codeine and tramadol (Figure 1). In clinical practice this is less clear. The production of the active metabolite of hydrocodone (hydromorphone) is reduced in CYP2D6 "poor metabolizers" but there is little evidence of a difference in analgesic effect. Ultra-rapid CYP2D6 metabolizers may have an increased response to hydrocodone with an increased risk of overdose. Approximately 26% is excreted in the urine either unchanged or as a metabolite; therefore, kidney failure is hoped to have only a minimal effect on drug clearance. However, data are extremely limited as described below. There is only a single study that has assessed the extent to which varying degrees of kidney failure can affect the pharmacokinetics of hydrocodone and this involved a single 45-mg dose of extended-release formulation over 144 h (45). All subjects received naloxone at 15 and 3 h before and 9 and 21 h post dose to minimize opioid-related adverse effects. There were eight patients with mild kidney failure (>50–80 ml/min), nine with moderate (30–50 ml/min), nine with severe (<30 ml/min), and nine on HD ≥6 mo. Systemic exposure was up to 70% greater in patients with moderate-to-severe kidney failure compared with patients with mild kidney failure but appeared to be unchanged in patients on HD. There was no consistent trend toward an increase in maximum concentration of hydrocodone with increasing severity of kidney failure. However, the incidence of adverse effects in patients on dialysis was similar to those with normal kidney function despite the concurrent use of naltrexone. Without any data to support its use and the high potential for unpredictable toxicity risk, it remains unclear the role that hydrocodone should or should not have in the pharmacologic management of pain for patients with advanced CKD.

NSAIDs, nonsteroidal anti-inflammatory drugs; SSRIs, selective serotonin reuptake inhibitors; COX, cyclooxygenase; CYP, cytochrome P450; M1, O-desmethyltramadol; M3G, morphine-3-glucuronide; M6G, morphine-6-glucuronide; HD, hemodialysis; Cmax, maximum concentration; AUC, area under the curve; HD, hemodialysis; CR, controlled release.

(20). Clinicians should be cautious about their use in patients with CKD due to increased risks of bleeding, cardiovascular events, psychiatric events, and kidney-related complications in those with residual kidney function (Table 4). NSAIDs are best reserved for specific indications of acute pain, limiting their use to the lowest effective dose and shortest duration (20). Avoiding the use of NSAIDs is associated with increased opioid use in an effort to control pain. Therefore, the risk profile of NSAIDs versus low-dose opioids needs to be ascertained for any given patient. Topical NSAIDs can provide effective pain relief without the systemic adverse events associated with oral NSAIDs when used for both acute and chronic pain (21,22). Where pain is present in joints or nonulcerated skin, this may be a useful alternative to oral administration.

Opioid Metabolism and Advanced CKD

Patients with kidney failure are at increased risk for adverse effects of opioids due to reduced elimination and increased accumulation of the parent analgesic and/or

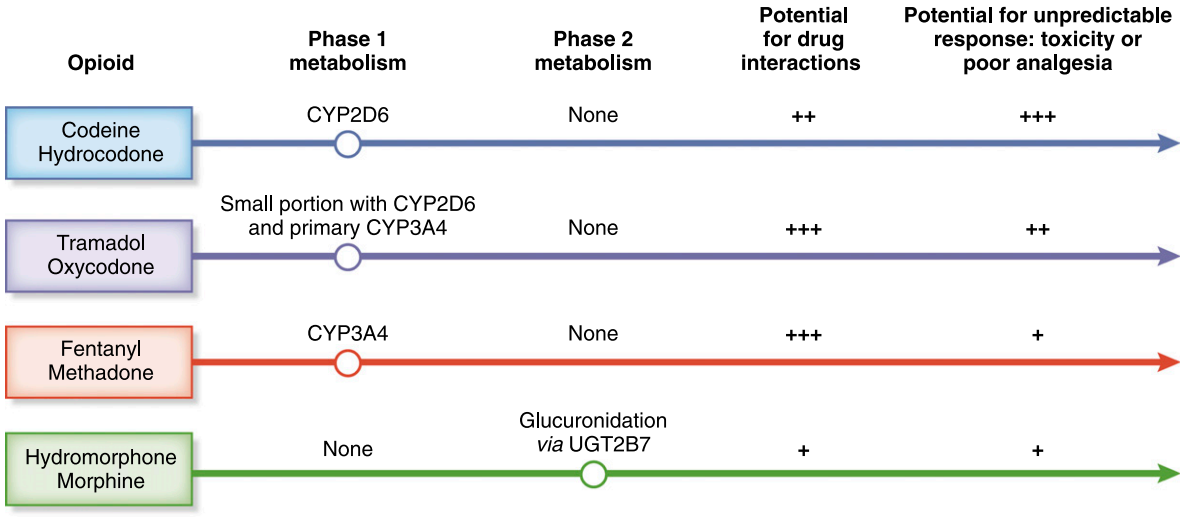

Figure 1. | Metabolic pathways for opioids involve either phase 1 or phase 2 metabolism, which impacts potential for drug interaction and unpredictable clinical response. CYP2D6, cytochrome P450 2D6 enzyme; CYP3A4, cytochrome P450 3A4 enzyme; UGT2B7, UDP-glucuronosyltransferase 2B7.

active metabolites. Analgesics may also be removed by dialysis, leading to uncertain analgesic effects during treatment.

The risks of opioid toxicity, poor analgesic response, and drug interactions are determined largely by which enzyme system(s) metabolizes the opioid and the patient's genetics factors and medical conditions (most notably, kidney or liver disease). Opioid metabolism takes place primarily in the liver, with the metabolites (and varying degrees of the parent drug) excreted by the kidneys. Opioid metabolism results in the production of both inactive and active metabolites, some of which may be more potent than the parent compound. These will accumulate to various degrees in patients with decreased kidney function and patients tend to have a narrow therapeutic window between analgesia and toxicity. Careful selection of opioids is

	CYP3A4	CYP2D6	Potential effect
Substrate	• Calcium channel blockers • Statins • Other cardiovascular agents (quinidine) • Benzodiazepines • Sleep aids: zopiclone, zolpidem • Psychiatric drugs: haloperidol, carbamazepine, mirtazapine • Macrolide antibiotics • HIV antivirals	• Beta-blockers • Antipsychotic drugs (haloperidol) • SNRIs • Tricyclic antidepressants • Histamine H1 receptor antagonists (metoclopramide) • Tamoxifen	May increase the parent opioid concentration, thereby prolonging analgesic effect or toxicity
Inhibitor	• Calcium channel blockers: specifically diltiazem and verapamil • Macrolide antibiotics • -azole antifungals • Grapefruit juice • Star fruit • HIV antivirals	• Antiarrhythmic agents: quinidine, amiodarone • SNRIs, SSRIs • Histamine H2 receptor antagonists: ranitidine, cimetidine • Bupropion • Cinacalcet	
Inducer	• Anticonvulsants: carbamazepine, phenytoin, barbiturates • Rifampin • St. John's wort	• Rifampin • Glucocorticoid: dexamethasone	May reduce opioid levels and therefore reduce analgesic effect

Figure 2. | Commonly used classes of drugs in patients with CKD that may act as substrates, inhibitors or inducers of CYP3A4 and CYP2D6 and therefore may affect opioid metabolism and effect. CYP2D6, cytochrome P450 2D6 enzyme; CYP3A4, cytochrome P450 3A4 enzyme; SNRIs, serotonin-norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

Table 5. The pharmacokinetics of opioids recommended for use in patients with advanced CKD

Characteristic	Hydromorphone	Fentanyl	Methadone	Buprenorphine
Clinical description	A potent μ receptor agonist that is approximately 5–7 times more potent than morphine after oral administration and approximately three times more potent after intravenous administration. It may cause less pruritus, sedation, and nausea than morphine.	A potent synthetic opioid that is 50–100 times more potent than morphine. It causes less histamine release, has a lower incidence of constipation, and affords greater cardiovascular stability than morphine.	A potent synthetic opioid with activity mainly at the μ receptor. It also appears to function as an NMDA receptor antagonist and therefore may be more effective for neuropathic pain than other strong opioids, although evidence to support this remains limited.	A potent semisynthetic opioid. It is a partial μ receptor agonist and a κ receptor antagonist.
Oral bioavailability	Low-to-moderate: 5%–35%	Low: usually administered intravenously or transdermally	High: >80%	Low: administered effectively sublingually or transdermally.
Route of clearance	Extensive first-pass hepatic metabolism with little unchanged drug found in the urine. It is metabolized principally to H3G, which has no analgesic activity but possibly causes neuro-excitation, agitation, confusion, and hallucinations. Unlike morphine, which has an active analgesic 6-glucuronide metabolite, H6G is present in trace amounts only. The pharmacokinetics of the active parent compound are not substantially altered by CKD, due to the rapid conversion to H3G (46).	Hepatic metabolism with 10%–20% excreted by the kidneys. Metabolites are inactive.	Hepatic metabolism into inactive metabolites with approximately 20% excreted unchanged in the urine. In patients who are anuric, methadone is exclusively excreted in feces with no significant accumulation in plasma (47).	Extensive first-pass hepatic metabolism with little unchanged drug found in the urine (48). The two major metabolites, B3G and norbuprenorphine, are mostly excreted fecally with only 10%–30% excreted in the urine (49). B3G is inactive with no analgesic properties. Norbuprenorphine is a less potent analgesic at the μ receptor than buprenorphine; its clinical relevance is thought to be limited because it does not cross the blood-brain barrier readily. A study with ten patients on HD showed no elevated buprenorphine or norbuprenorphine plasma levels after receiving transdermal buprenorphine (median dose 52.5 μg/h) for at least 1 wk (50).
Plasma $t_{1/2}$	Hydromorphone: unchanged with CKD. H3G: prolonged—33 h	Unchanged with CKD.	Unchanged with CKD. However, prolonged pharmacologic action due to slow release from tissue reservoirs of up to 60 h (51).	Unchanged with CKD.
Volume of distribution	Low: 1.22 L/kg	High: 2–5 L/kg	High: 4.1–6.7 L/kg	Very high, greater than physiologic volumes. Estimated to be 188–430 L after iv administration (transdermal unknown).
Serum protein binding	Low: 19%	High: 79%	High: 60%–90%	High: 96%
Water solubility	High	Low (lipophilic): suitable for a transdermal delivery	Low (lipophilic): suitable for a transdermal delivery	High
mol wt	Low: 285.3 g/mol	Low: 336.5 g/mol	Low: 309.5 g/mol	Low: 467.6 g/mol

Table 5. (Continued)

Characteristic	Hydromorphone	Fentanyl	Methadone	Buprenorphine
Removal by HD	H3G accumulates between dialysis treatments but appears to be effectively removed during HD with no significant change in pain scores post HD or a need for supplemental dosing (46,52).	Not removed to any significant degree but there is the possibility of adsorption to CT190 dialysis membranes (53).[a]	Parent drug and metabolites do not seem to be removed by HD: approximately 6.0%–14.9% reductions in plasma methadone (52,54,55). No significant difference in pain scores post HD and supplemental methadone is not required post HD (52). Q-T interval increased significantly: maximum 152 min after methadone intake. Remained <500 ms and was not linearly associated with serum methadone concentration—but may be exacerbated by HD reductions in serum potassium and/or magnesium (54).	HD does not appear to affect buprenorphine plasma levels, and analgesic effect is stable during HD (50).
Dosing recommendations	Start at 0.5 mg by mouth (or 0.2 mg subcutaneously) every 4–6 h.	Not recommended in opioid-naïve patients. When converting from hydromorphone, 6–8 mg oral hydromorphone daily can be converted to 12 μg/h transdermally every 72 h.	Start 1–2 mg every 12–24 h by mouth. Obtain a pretreatment ECG and a follow-up ECG 2–4 wk after initiation to monitor for prolonged Q-T interval.	Start at 5 μg/h transdermally every 7 d.

NMDA, N-methyl-D-aspartate; H3G, hydromorphone-3-glucuronide; H6G, hydromorphone-6-glucuronide; B3G, buprenorphine-3-glucuronide; HD, hemodialysis; ECG, electrocardiogram.
[a]On the basis of data from a single patient receiving maintenance hemodialysis.

essential, and understanding opioid metabolism is important in this determination.

There are two forms of metabolism that occur in the liver: phase 1 metabolism, which typically subjects the drug to oxidation or hydrolysis; and phase 2 metabolism, which conjugates the drug. Opioids may undergo phase 1 metabolism, phase 2 metabolism, or both (Figure 1) (23,24). Phase 1 metabolism involves primarily the cytochrome P450 2D6 (CYP2D6) and cytochrome P450 3A4 (CYP3A4) enzymes.

There is tremendous genetic polymorphism of the *CYP2D6* gene. Individuals who have three or more active copies of the *CYP2D6* gene are described as "ultra-rapid metabolizers." Conversely, those who carry inactive copies of *CYP2D6* are "poor metabolizers." An individual's response is highly variable and can result in unpredictable toxicity with trivial doses or poor analgesic response with standard doses (25).

The CYP3A4 enzyme metabolizes >50% of drugs so opioids metabolized by this enzyme have a high risk of drug-drug interactions. Concomitant use of CYP3A4 substrates and inhibitors can increase the parent opioid concentration, thereby prolonging analgesic effect or toxicity. Examples can be seen in Figure 2. CYP3A4 inducers can reduce opioid levels and therefore reduce analgesic effect. The CYP2D6 enzyme metabolizes approximately 25% of drugs so is associated with a lower risk of drug-drug interactions.

Drugs that are metabolized by phase 2 glucuronidation, such hydromorphone, have minimal drug interaction potential. Although genetic variability exists, the clinical relevance is unknown and these drugs do not appear to have the same risk for unpredictable toxicity as seen with CYP2D6-mediated metabolism.

The Effect of Dialyzability of Analgesics on Pain Management

Stability of analgesia during dialysis will vary among different analgesics. Opioids that are well dialyzed will

likely require supplemental dosing during or after HD and patients could be at higher risk for opioid withdrawal symptoms after dialysis. Opioids that are not well dialyzed will have more stable analgesia. However, if there is accumulation of the parent drug and/or active metabolites, the risk for toxicity increases. The ability of dialysis to remove any drug depends upon several factors. Factors that promote dialyzability include lower mol wt, lower protein binding, greater water solubility, and lower volume of distribution.

Recommended Opioids for Pain Management in Patients with Advanced CKD

The opioids felt to be the safest for patients with advanced CKD and their pharmacokinetic properties are outlined in Table 5. Given the minimal changes in kinetics in kidney failure, hydromorphone, fentanyl, methadone, and buprenorphine may be potentially useful opioids. They appear to have stable analgesic affect during HD. Hydromorphone has the advantage of undergoing no phase 1 metabolism, therefore avoiding the complications of unpredictable toxicity and drug-drug interactions seen with the CYP2D6- and CYP34A-metabolized opioids. More than 80% of 55 patients with cancer and kidney failure who experienced adverse effects, primarily with morphine, improved after a switch to hydromorphone (26). Methadone and fentanyl do not produce active metabolites. The metabolism of methadone relies on several CYP enzymes in addition to CYP3A4 so the potential for drug-drug interactions is complex. Methadone also interacts with the voltage-gated potassium channels of the myocardium and can prolong Q-T intervals. Not every patient experiences Q-T interval prolongation with methadone, but risk factors include female sex, hypokalemia, high-dose methadone, drug interactions, and underlying cardiac conditions. It is generally recommended to limit the use of methadone to experienced prescribers. Caution is required when using buprenorphine because the reversal of buprenorphine-induced respiratory depression may be delayed and inconsistent, requiring large doses of naloxone, due to the slow association and dissociation between buprenorphine and opioid receptors, which limits the ability of naloxone to displace buprenorphine from the receptors (27). Unfortunately, clinical studies are lacking to support their efficacy and safety, especially as they relate to chronic pain management.

Putting It All Together: A General Approach to the Pharmacologic Management of Pain for Patients with Advanced CKD

A cautious stepwise approach to the introduction and titration of analgesics is outlined in Figure 3. For patients with a neuropathic component to their pain, the first step is to introduce an adjuvant. The pharmacokinetics and pharmacodynamics of recommended adjuvants in patients with advanced CKD are outlined in Table 6.

Anticonvulsants and tricyclic antidepressants are the two classes of drugs for which there is most evidence of efficacy. Systematic reviews have found that anticonvulsants and tricyclic antidepressants are effective in reducing neuropathic pain due to diabetic peripheral neuropathy

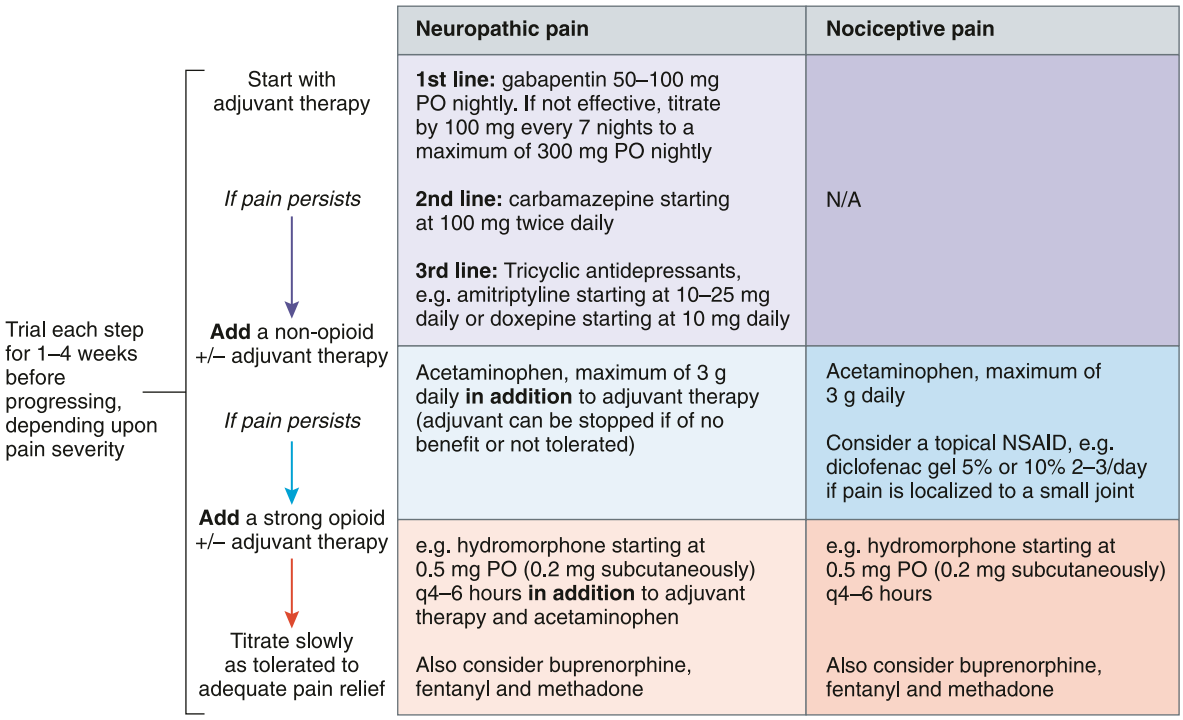

Figure 3. | **Pharmacological management of pain in patients with advanced CKD requires a cautious stepwise approach.** N/A, not applicable; NSAID, nonsteroidal anti-inflammatory drug; PO, by mouth; TCAs, tricyclic antidepressants.

Table 6. The pharmacokinetics of recommended adjuvants for the treatment of neuropathic in patients with advanced CKD

Characteristic	Gabapentin (56,57)	Pregabalin (57,58)[a]	Carbamazepine (59)	Amitriptyline (60,61)	Ketamine (62,63)
Clinical description	Gabapentin is an analog of the neurotransmitter GABA with high-affinity binding to the $\alpha_2\delta$ protein. It reduces the release of excitatory neurotransmitters from the brain although does not have activity at GABA receptors. It has analgesic and anticonvulsant activity.	Pregabalin is also an analog of the neurotransmitter GABA with high-affinity binding to the $\alpha_2\delta$ protein. It reduces the release of excitatory neurotransmitters from the brain but has no activity at GABA receptors. It has analgesic, anxiolytic, and anticonvulsant activity.	Carbamazepine is an anticonvulsant used to treat seizure disorders and neuropathic pain. It is a tricyclic compound chemically related to TCAs and also functions as a mood stabilizer.	Amitriptyline is a TCA with sedative effects that is used to treat major depressive and anxiety disorders as well as migraines and neuropathic pain.	Ketamine is an anesthetic with analgesic, anti-inflammatory, and antidepressant properties when used in subanesthetic doses. It is a potent NMDA receptor channel antagonist. Its use is typically reserved for intractable neuropathic pain resistant to opioids and other adjuvants.
Oral bioavailability	High-to-moderate: approximately 80% at up to 300 mg daily but decreases with increasing dose, particularly with doses >900 mg daily.	High: >90% irrespective of dose	High: approximately 89%	Low-to-moderate due to extensive first-pass hepatic metabolism: approximately 33%–62%	Low due to extensive first-pass hepatic metabolism: 16%–29%
Peak plasma concentration	Approximately 3 h	Approximately 1 h	Approximately 6 h	Approximately 6 h	Oral: 20–120 min iv: <5 min
Route of clearance	Not appreciably metabolized and >95% is excreted unchanged by the kidneys. No inhibition of the enzyme systems responsible for the metabolism of other drugs.	Not appreciably metabolized and >95% is excreted unchanged by the kidneys. No inhibition of the enzyme systems responsible for the metabolism of other drugs.	Metabolized in the liver *via* phase 1 metabolism primarily by CYP3A4. The metabolites are excreted *via* the kidneys with approximately 20%–30% excreted *via* the feces. Only 3%–5% is excreted unchanged by the kidneys.	Extensively metabolized on first pass through the liver. It undergoes phase 1 metabolism primarily by CYP2D6 and CYP3A4.	Extensively metabolized on first pass through the liver. It undergoes phase 1 metabolism primarily by CYP3A4 and CYP2B6 to its two principal metabolites norketamine (has analgesic properties) and hydroxynorketamines (may have low potency antidepressant effects) before being further metabolized to mostly inactive dehydronorketamine. Metabolites are cleared by the kidneys with low levels cleared as ketamine (2%), norketamine (2%), and dehydronorketamine (16%). Most (80%) is cleared as hydroxynorketamines.
Plasma $t_{1/2}$	Increases linearly with decreased kidney function.	Increases linearly with decreased kidney function. Cl_{Cr}>60 ml/min=9 h Cl_{Cr} 30–60 ml/min=17 h Cl_{Cr} 15–29 ml/min=25 h Cl_{Cr}<15 ml/min=49 h On hemodialysis 3/wk=55 h	Approximately 35 h; remains unchanged with ESKD.	Highly variable at 10–28 h; remains unchanged with ESKD.	2–4 h
Serum protein binding	Not bound to plasma proteins	Not bound to plasma proteins	70%–80%	Highly bound to plasma and tissue proteins	10%–50%
Water solubility	High	High	High	Low; highly lipophilic	High

Table 6. (Continued)

Characteristic	Gabapentin (56,57)	Pregabalin (57,58)[a]	Carbamazepine (59)	Amitriptyline (60,61)	Ketamine (62,63)
Removal by HD	Well dialyzed. Approximately 50% of serum drug is removed during a 4-h session. Supplemental dosing postdialysis may be required. Gabapentin is also cleared by continuous ambulatory PD although this is a slow method to treat toxicity (31).	Well dialyzed. Approximately 50% of serum drug is removed during a 4-h session. The $t_{1/2}$ during dialysis treatment is approximately 3 h. Supplemental dosing post HD may be required.	Dialyzed. Clearance in the era of low flux HD membranes is twice the endogenous plasma clearance. However, it appears that supplemental dosing post HD is not required because of the long elimination $t_{1/2}$ of carbamazepine of 35 h compared with a 4-h session.	Not dialyzed with HD or PD	Not studied in dialysis
Dosing recommendations	Dose post HD. Below are maximum recommended doses. It may be reasonable, especially for older patients, or those with moderate rather than severe neuropathic pain, to start with doses as low as 100 mg postdialysis or 100 mg every second night in patients with stage 5 CKD managed conservatively. eGFR 50–79 ml/min: 600 mg three times per d eGFR 30–49 ml/min: 300 mg three times per d eGFR<15 ml/min: 300 mg once per d	Dose post HD. Below are maximum recommended doses. It may be reasonable, especially for older patients, or those with moderate rather than severe neuropathic pain, to start with doses as low as 25 mg post HD or 25 mg every second night in patients with stage 5 CKD managed conservatively. eGFR>30–60 ml/min: 150 mg twice per d eGFR 15–30 ml/min: 150 mg once per d eGFR 15–29 ml/min: 300 mg twice per d	Start at 100 mg daily or twice daily and increase by 100 mg daily to a maximum of 1200 mg daily.	Although no dose reduction is required, a low starting dose of approximately 25 mg nightly is recommended given the likelihood of anticholinergic adverse effects such as blurred vision, dry mouth, and constipation.	Given the pharmacokinetic, no dose reduction is required. By mouth: 0.5 mg/kg twice daily or 2 mg/kg daily Subcutaneously: 0.05–0.15 mg/kg per h for up to 7 d iv: 0.15–0.25 mg/kg To reduce the adverse effects of psychosis and tachycardia, the concurrent administration of haloperidol or midazolam is recommended.

GABA, γ-aminobutyric acid; $\alpha_2\delta$ protein, α-2-δ protein; TCA, tricyclic antidepressant; NMDA, N-methyl-D-aspartate; CYP, cytochrome P450; Cl_{Cr}, creatinine clearance; HD, hemodialysis; PD, peritoneal dialysis.
[a]On the basis of a single dose of 50 mg of pregabalin in an open-label, parallel-group study.

and postherpetic neuralgia (28,29). The evidence for effectiveness for other causes of neuropathic pain is too limited to provide strong conclusions, although small studies in patients on HD have shown improvement in pain and QOL scores for diverse causes of neuropathic pain using gabapentin (30). Gabapentin is structurally similar to the neurotransmitter γ-aminobutyric acid but, rather than bind to γ-aminobutyric acid receptors, its mechanism of action is thought to be through binding to calcium channels and modulating the influx of calcium. Gabapentin is almost exclusively cleared by the kidneys and substantial dose reduction is required as the GFR declines to avoid toxicity (Table 6). Adverse effects include somnolence, dizziness, peripheral edema, and gait disturbances.

Evidence suggests that carbamazepine may be as effective as gabapentin for treating neuropathic pain in the general population and may have fewer adverse effects. Unlike gabapentin, it requires no dose adjustment in CKD as outlined in Table 6 (31). Tricyclic antidepressants are effective in the management of neuropathic pain but are less well tolerated than the gabapentinoids in patients with CKD because of anticholinergic, histaminergic, and adrenergic side effects resulting in symptoms such as dry mouth, orthostatic hypotension, and somnolence. Although dose reduction of tricyclic antidepressants is not necessarily required, patients with CKD will often respond to lower doses.

Ketamine is an anesthetic agent that functions as an analgesic in subanesthetic doses. Clinically, it is reserved for intractable neuropathic pain that is resistant to basic adjuvants and opioids. An example is the management of the pain of calciphylaxis. There is no need for dose adjustment in CKD. However, adverse events such as tachycardia and psychosis may limit its use. To reduce this risk the concurrent administration of haloperidol or midazolam is recommended (Table 6).

There are insufficient data or clinical experience with selective serotonin reuptake inhibitors and selective serotonin-norepinephrine reuptake inhibitors for

neuropathic pain in CKD to make a recommendation. In the general population they tend to be less effective than anticonvulsants and tricyclic antidepressants but have fewer adverse effects (28,29).

Nonopioids should be used as initial pharmacologic management for nociceptive pain and for neuropathic pain if pain persists despite maximal tolerated dose of an adjuvant. Studies have failed to show that a weak opioid has markedly superior analgesic efficacy to acetaminophen or an NSAID.

Before starting an opioid, consider completing an assessment tool such as the Screener and Opioid Assessment for Patients with Pain–Revised to assess the risk for aberrant opioid-related behavior (32). Those that are categorized as having a high risk of future abusive drug-related behavior would benefit from referral to a pain specialist for management of their pain and opioid prescribing.

Although the initial WHO analgesic ladder advocates for trialing weak opioids before starting a strong opioid, there is no evidence that weak opioids such as codeine and tramadol are less risky than strong opioids at their lowest effective dose (Table 4) (33). The response to these weak opioids varies highly from one patient to another, with an unpredictable risk of fatal overdosing with trivial doses or poor analgesic effect after administration of standard doses (Table 4) (25). The "weak" opioids also have dose-dependent adverse effects similar to the strong opioids. A recent United States study of 140,899 patients on HD showed that the highest hazards for altered mental status, falls, and fractures among all opioids prescribed were associated with codeine (16). In addition, there is no evidence that at equivalent analgesic efficacy weak opioids carry a lower risk of addiction than low-dose strong opioids. Therefore, given the risks of using weak opioids such as codeine and tramadol in patients with advanced CKD, it seems more prudent to use to a strong opioid at a low dose with careful titration when opioid therapy is required (33).

Adverse effects of opioids are common and will prevent effective analgesia if not well managed. Constipation is persistent and nearly universal and patients should have a bowel routine, *e.g.*, PEG 3350 prescribed pre-emptively. Nausea and vomiting occur in about 50% of people, wearing off in most after 7–10 days. The central nervous system effects occur most frequently on initiating opioids and when increasing the dose, hence the need to "start low and titrate slow." Respiratory depression is unusual if oral, short-acting preparations are used and the dose is titrated against pain and toxicity: pain is said to be the physiologic antagonist of opioids. When pain is stable, opioids can be used in long-acting preparations such as transdermal fentanyl or methadone. As a patient's condition deteriorates, especially nearer the end of life, swallowing becomes compromised and alternate routes are required, such as subcutaneous fentanyl. Hallucinations, a very distressing adverse effect, may occur and should be managed by dose reduction, switching to an alternative opioid, or with coadministration of haloperidol.

Summary

Pain is highly complex, which is further compounded by kidney failure: a simple approach will not be sufficient. Analgesics play an important role in pain management but they should not be the sole focus of treatment, especially for patients with chronic pain where the somatosensory component of the pain tends to assume greater importance than the original trigger. Nonpharmacologic therapies that address the whole person in the context of their disease and personal life are a vital part of managing chronic pain and analgesics should only be used to augment these therapies as required to achieve adequate relief. The pharmacologic management of pain for patients with CKD requires careful selection of analgesics with close attention to efficacy and safety, keeping in mind that the overall goal is to promote function and QOL and not necessarily completely resolve the pain. To date, there are no studies that look at clinical outcomes of chronic analgesic use in patients with CKD. This will clearly need to change if we are to optimize safe and effective management of pain for our patients.

Disclosures

None.

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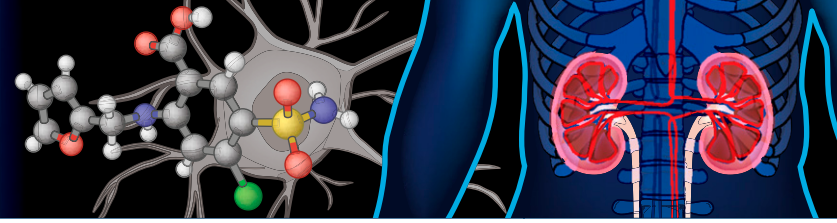

Clinical Pharmacology of Antibiotics

Rachel F. Eyler[1,2] *and Kristina Shvets*[2]

Abstract

Antimicrobial pharmacology and its effect on prescribing is quite complex. Selecting an antibiotic that will optimally treat an infection while minimizing adverse effects and the development of resistance is only the first step, as one must also consider the patient's individual pharmacokinetic alterations and the pharmacodynamic properties of the drug when prescribing it as well. Patients with CKD may have alterations in their protein binding, volumes of distribution, kidney clearance, and nonrenal clearance that necessitates antibiotic dose adjustments to prevent the development of toxicity. Knowledge of a drug's pharmacodynamics, defined as the relationship between drug exposure and antibacterial efficacy, provides some guidance regarding the optimal way to make dose adjustments. Different pharmacodynamic goals, such as maximizing the time that free (unbound) drug concentrations spend above the minimum inhibitory concentration (MIC) for time dependent drugs (*e.g.*, β-lactams) or maximizing the free peak-to-MIC ratio for concentration-dependent antibiotics (*e.g.*, aminoglycosides), require different adjustment strategies; for instance, decreasing the dose while maintaining normal dosing frequency or giving normal (or even larger) doses less frequently, respectively. Patients receiving hemodialysis have other important prescribing considerations as well. The nephrologist or patient may prefer to receive antibiotics that can be administered intravenously toward the end of a dialysis session. Additionally, newer dialysis technologies and filters can increase drug removal more than originally reported. This review will discuss the place in therapy, mechanism of action, pharmacokinetic, pharmacodynamic, and other pharmacologic considerations encountered when prescribing commonly used antibiotics in patients with chronic kidney disease or ESKD.

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Introduction

Infections are common in patients with CKD, especially in those with ESKD (1). In a United States Medicare cohort of patients newly started on hemodialysis between 1996 and 2001, the 12-month incidence of infection-related hospitalization was 32% (1,2). Antibiotic optimization in CKD and ESKD can often be quite complicated, as these patients may have altered pharmacokinetics (absorption, distribution, metabolism, and elimination) and are often at increased risk of side effects (3,4). Dialysis comes with additional considerations as well, as there are periods of increased clearance during dialysis followed by 48–72 hours of relatively little antibiotic clearance between dialysis sessions. Additionally, many studies of drug removal by dialysis were conducted in the 1980s, when low-flux filters were used and high-flux filters (commonly used today) were only considered as experimental treatments (5).

In addition to patient-specific and dialysis-related considerations, there are drug-related considerations. The study of pharmacodynamics relates drug exposure to antibacterial activity (6), and identifies pharmacodynamic parameters such as the maximum concentration (peak)-to-MIC ratio, percentage of the dosing interval that concentrations stay above MIC (time>MIC), and the drug exposure-to-MIC ratio (area under the curve [AUC]:MIC), which correlate well with therapeutic efficacy. The pharmacodynamic parameters are depicted on a concentration-time curve in Figure 1. In general antibiotics can be categorized as time-dependent killers or concentration-dependent killers (Table 1). When dosing time-dependent antibiotics (*e.g.*, β-lactams), it is important to maximize time>MIC, whereas when dosing concentration-dependent antibiotics (*e.g.*, aminoglycosides), the peak:MIC ratio is the most important pharmacodynamic parameter to optimize (6). Hence, when making dose adjustments for kidney disease, knowing the pharmacodynamic properties of antibiotics can help guide the clinician when deciding whether to decrease the dose and keep the dosing frequency constant (often preferred with time-dependent antibiotics) or keep the dose the same and prolong the dosing interval (often preferred with concentration-dependent antibiotics).

Pharmacologic considerations, including discussions of place in therapy, mechanism of action, pharmacokinetics, and pharmacodynamics, when prescribing commonly used classes of antibiotics in patients with CKD and ESKD will be reviewed.

β-Lactam Antibiotics

The penicillin, cephalosporin, and carbapenem antibiotics all contain a β-lactam ring and work by inhibiting the last step in bacterial cell-wall peptidoglycan synthesis (7) (Figure 2). The individual β-lactam spectrums of activity and commonly treated infectious diseases are summarized in Table 2. β-lactams exhibit time-dependent pharmacodynamics (6), and so when adjusting these medications for kidney disease, it is

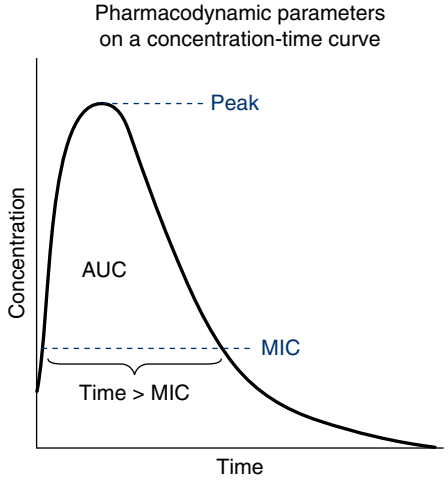

Figure 1. | Pharmacodynamic parameters on a concentration–time curve. Peak:MIC is the parameter to optimize for concentration-dependent antibiotics. Time>MIC is the parameter to optimize for time-dependent antibiotics.

often preferable to decrease the dose while maintaining the dosing interval. Interestingly, CKD actually makes it somewhat easier to achieve pharmacodynamic targets with time-dependent antibiotics because the extended $t_{1/2}$ of β-lactams in these patients prolongs the length of time that concentrations will remain above the MIC. In recent years, a loading dose followed by extended or continuous infusions of β-lactams (*e.g.*, piperacillin-tazobactam [8], ceftazidime, cefepime, meropenem, and doripenem [9]) have been proposed to maximize the time that concentrations stay above MIC.

When doses of β-lactams have not been adjusted appropriately, central nervous system (CNS) disturbances such as confusion, myoclonus, and seizures can occur (10). This is primarily presumed to be because of decreased kidney clearance leading to higher than normal concentrations of β-lactams in the CNS. Characteristics of uremic patients, including decreased protein binding of β-lactams (leading to higher free fractions of the drug), as well as uremia-induced physiologic changes to the cerebrum may predispose patients to these effects (10).

Penicillins

Despite increasing antimicrobial resistance, the penicillins continue to play a valuable role in modern antibiotic therapy. Many penicillins have a short $t_{1/2}$ (usually about 0.5–1.5 hours in patients with normal kidney function) because of a low volume of distribution combined with significant kidney tubular secretion (7). The high kidney secretion rate can lead to some interesting dosing difficulties. For example, in one study of ampicillin, it was found that the six patients with GN who had mildly reduced creatinine clearance but normal tubular secretion required full doses of the drug. On the other hand, in the 11 patients with impaired kidney function, tubular secretion decreased in parallel with the severity of the disease, and patients required lower doses than would be predicted by a decrease in creatinine clearance alone (11). The authors concluded that new dosage adjustment methods that incorporate both glomerular and tubular function were needed. Unfortunately, no clinically practical approaches to individualize drug dosing on the basis of tubular secretion have been developed (12).

Penicillins are generally well tolerated in patients with kidney disease. Hypersensitivity reactions are commonly reported, and an association between penicillins and interstitial nephritis exists, but patients with kidney disease are not considered to be at higher risk (10). Piperacillin-tazobactam, a penicillin antibiotic that is not commonly associated with nephrotoxicity, has more recently been associated with AKI when combined with vancomycin (13). The mechanism behind this association, however, remains unclear (13). Penicillin G, carbenicillin, ticarcillin, and ampicillin have been associated with impaired platelet aggregation, a rare side effect that may be more likely in patients with uremia-induced platelet dysfunction (7,10).

Cephalosporins

One niche of the first generation cephalosporins is in treating catheter-related bacteremias due to methicillin-susceptible *Staphylococcus aureus* (MSSA). Once it becomes clear that the organism is MSSA, β-lactam agents are associated with better outcomes than vancomycin therapy (14). Cefazolin is a reasonable choice as it may be administered three times a week, after dialysis sessions (14,15).

Table 1. Pharmacodynamics of common antibiotic classes (5,6)

Antibiotic Class	Pharmacodynamic Profile	Pharmacodynamic Parameter to Optimize
Aminoglycosides	Concentration-dependent	Peak:MIC
Penicillins	Time-dependent	Time>MIC
Cephalosporins	Time-dependent	Time>MIC
Carbapenems	Time-dependent	Time>MIC
Vancomycin	Time-dependent	AUC:MIC
Lipopeptides	Concentration-dependent	AUC:MIC; peak:MIC
Oxazolidinones	Time-dependent	AUC:MIC
Lipoglycopeptides	Concentration-dependent	AUC:MIC
Fluoroquinolones	Concentration dependent	AUC:MIC
Macrolides	Time-dependent	AUC:MIC
Sulfamethoxazole-trimethoprim	Limited data (65)	Limited data (65)

Peak:MIC, maximum concentration (peak)-to-minimum inhibitory concentration ratio; Time>MIC, percentage of the dosing interval that concentrations stay above the minimum inhibitory concentration; AUC:MIC, drug exposure (area under the curve)-to-minimum inhibitory concentration ratio.

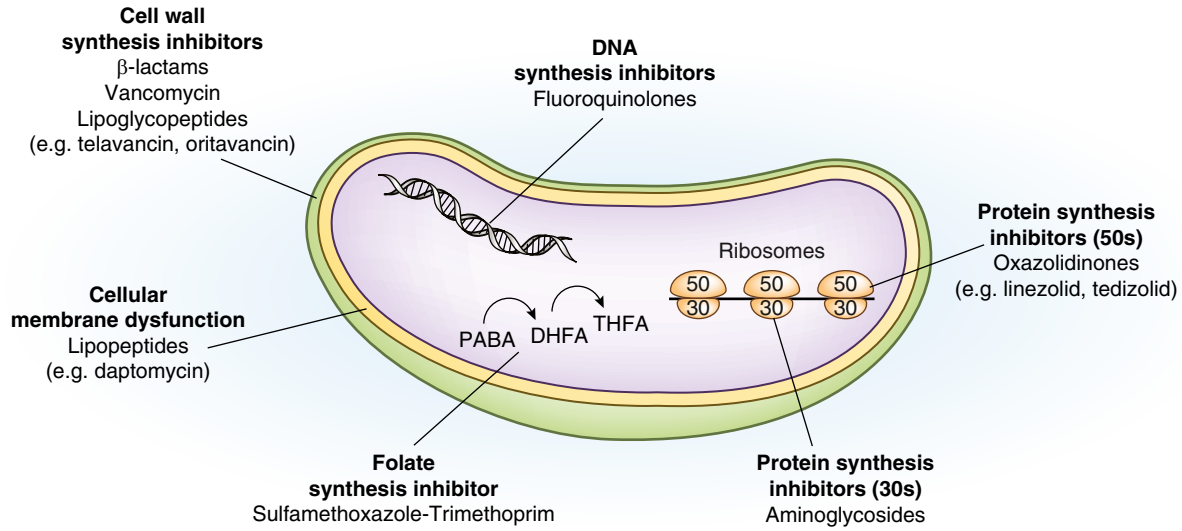

Figure 2. | **Mechanisms of antibiotic classes.**

Gram-negative bacilli are responsible for 14%–27% of bloodstream infections in hemodialysis patients (16,17). When treating Gram-negative infections, third and fourth generation cephalosporins are utilized because of their increased activity against Gram-negative organisms. Ceftazidime is a useful option as it can be dosed three times a week, after hemodialysis sessions, to achieve pharmacodynamic targets (18). There is limited data on the pharmacodynamics of ceftazidime in humans, but an analysis of a phase 3 study found that patients with ceftazidime concentrations above MIC for 45% of the dosing interval (45% time>MIC) achieved more favorable outcomes in patients with hospital-acquired pneumonia. In more critical infections or in neutropenia, where one might desire to use even more conservative pharmacodynamic targets (70% time>MIC), it may be better to dose the medication once daily (18).

Carbapenems

Further structural modifications to the β-lactam backbone gave rise to the carbapenem class of antibiotics and conferred a broader spectrum of activity, including activity against β-lactamase producing Gram-negative organisms. (7). Imipenem, the first drug in the class, is associated with seizures in high doses and so should be used cautiously in those with CNS lesions, neurologic disorders, or kidney disease. In the largest review of imipenem-adverse effects (looking at 3470 patients in phase 3 clinical trials), an overall seizure rate of 2% was reported (19). In phase 3 noncomparative trials, when looking specifically at patients with creatinine clearance <20 ml/min the incidence of seizures was 11.8% in patients receiving doses of 0.5–1.9 g/d and 16.1% in patients receiving >3 g/d (20).

The seizure risks for meropenem, doripenem, and ertapenem are reported at <1%, although all carbapenems have warnings about seizures listed in their prescribing information (20). At the same time that carbapenems raise seizure risk (hypothesized to be due to binding to GABA receptors), carbapenems also dramatically decrease valproic acid levels. Although the mechanism is unclear (proposed mechanisms include decreased absorption of valproic acid due to carbapenem-induced inhibition of intestinal transporters, decreased enterohepatic circulation of valproic acid due to decreased gut bacterial β-glucuronidase, and increased distribution of valproic acid in erythrocytes [21,22]), a review of six cases of concomitant carbapenem and valproic acid use found that valproic acid concentrations fell by an average of 81.2%, with the lowest concentration measured between day 4 and day 11 of carbapenem therapy (21). Carbapenems are generally well tolerated, with common adverse effects including infusion site complications, diarrhea, nausea, and vomiting (7).

Antimethicillin-Resistant *S. Aureus* Agents

Vancomycin

Vancomycin is a glycopeptide antibiotic with activity against the majority of Gram-positive bacteria (Table 3). It inhibits bacterial cell-wall synthesis through high-affinity binding to D-alanyl-D-alanine cell-wall precursor units (23). Because of its primarily bacteriostatic profile, vancomycin should be used as a second-line drug to bactericidal β-lactam antibiotics, like cefazolin and oxacillin, in serious Gram-positive infections such as MSSA bacteremias. Vancomycin is eliminated by the kidneys with 90% excreted as unchanged drug (23). On the basis of data from animal, *in vitro*, and human studies, research suggests that the AUC:MIC ratio is the pharmacodynamic parameter linked to vancomycin effectiveness (24). Clinically, vancomycin serum trough concentration monitoring is used as the surrogate marker for AUC for convenience and practicality; however, this has not been validated in a large cohort of patients on dialysis (24–26).

In clinical practice, vancomycin is the first-line agent for the treatment of serious methicillin-resistant *S. aureus* infections. Increased vancomycin use has resulted in the emergence of *S. aureus* isolates with reduced vancomycin susceptibility. Subsequently, the Clinical and Laboratory Standards Institute lowered MIC susceptibility breakpoints from 4 to 2 μg/ml. Targeting higher vancomycin trough concentrations (15–20 μg/ml) has

Table 2. β-Lactam antibiotic spectrum of activity and infectious diseases treated (7)

Antibiotic Class	Spectrum of Activity		Commonly Treated Infectious Diseases
	Gram-Positive	Gram-Negative	
Penicillin	β-Hemolytic streptococci +++ Viridans streptococci ++ *Streptococcus pneumoniae* ++	No activity	Pharyngitis Endocarditis Neurosyphilis Osteomyelitis
Aminopenicillins Amoxicillin Ampicillin	See penicillin, plus *Enterococcus faecalis* +++ *Listeria monocytogenes* +++	*Haemophilus influenza* ++ *Escherichia coli* + *Proteus mirabilis* +	Pharyngitis Lower respiratory tract infections Genitourinary tract infections Skin/skin structure infections Endocarditis (ampicillin) Osteomyelitis (ampicillin) Prosthetic joint infection (ampicillin)
Aminopenicillins with β-lactamase inhibitors Amoxicillin-clavulanate Ampicillin-sulbactam	See aminopenicillins, plus MSSA ++	*Proteus mirabilis* +++ *Haemophilus influenzae* +++ *Escherichia coli* ++ *Moraxella catarrhalis* ++ *Klebsiella sp.* ++ *Acinetobacter* sp. + (sulbactam component) Anaerobes: *Bacteroides fragilis* +++	Bite wounds (animal/human) Pneumonia, community-acquired Intra-abdominal infections Urinary tract infections Diabetic foot infections
Antipseudomonal penicillins Piperacillin-tazobactam	See aminopenicillins and aminopenicillins with β-lactamase inhibitors, plus	*Escherichia coli* +++ *Klebsiella* sp. +++ *Enterobacter* sp. ++ *Citrobacter* sp. ++ *Pseudomonas aeruginosa* ++	Bloodstream infections (Gram-negative bacteremia) Intra-abdominal infections Diabetic foot infections Febrile neutropenia Pneumonia, hospital-acquired or ventilator-associated Sepsis and septic shock (broad-spectrum coverage) Urinary tract infections, complicated Skin and soft tissue infection, necrotizing (broad-spectrum coverage)
Cephalosporins First generation *Cephalexin* *Cefazolin*	Streptococci +++ MSSA +++	*Escherichia coli* ++ *Klebsiella sp.* ++ *Proteus mirabilis* ++	Endocarditis (cefazolin) Osteomyelitis (cefazolin) Skin and soft tissue infections Bloodstream infections, MSSA (cefazolin) Pharyngitis Urinary tract infections, uncomplicated

Table 2. (Continued)

Antibiotic Class	Spectrum of Activity		Commonly Treated Infectious Diseases
	Gram-Positive	Gram-Negative	
Second generation *Cefoxitin* *Cefotetan* *Cefuroxime*	Streptococci ++ MSSA ++	*Haemophilus influenzae* ++ *Moraxella catarrhalis* ++ *Proteus* sp. ++ *Escherichia coli* ++ *Klebsiella sp.* ++ *Bacteroides fragilis* ++ (cefoxitin, cefotetan)	Intra-abdominal infections Pneumonia, community-acquired (cefuroxime) Skin/skin structure infections Urinary tract infections Pharyngitis
Third generation *Cefdinir* *Cefotaxime* *Ceftriaxone*	Streptococci +++ MSSA ++	*Haemophilus influenzae* +++ *Proteus* sp. +++ *Escherichia coli* +++ *Klebsiella sp.* +++ *Serratia* sp. +++ *Citrobacter* + *Enterobacter* +	Intra-abdominal infections (with metronidazole) Gonorrhea (cefotaxime) Pneumonia, community-acquired Spontaneous bacterial peritonitis Urinary tract infections Pyelonephritis Meningitis
Antipseudomonal cephalosporins Cefepime Ceftazidime Ceftazidime/avibactam Ceftolozane/tazobactam	See third generation, plus MSSA +++ Note: ceftazidime, ceftazidime/avibactam and ceftolozane/tazobactam have poor coverage of Gram-positive organisms	*Enterobacter* ++ (cefepime, ceftazidime/avibactam) *Pseudomonas aeruginosa* ++	Febrile neutropenia (cefepime) Intra-abdominal infections (with metronidazole) Pneumonia, hospital-acquired or ventilator-associated Urinary tract infections Osteomyelitis Infections by ESBL/KPC-producing Enterobacteriaceae (ceftazidime/tazobactam)
Anti-MRSA cephalosporins Ceftaroline	See third generation, plus MSSA/MRSA +++		Pneumonia, community-acquired Skin/skin structure infections
Carbapenems Imipenem-cilastatin Meropenem Doripenem Ertapenem	Streptococci +++ MSSA +++ *Enterococcus faecalis* (imipenem) ++	*Haemophilus influenzae* +++ *Proteus* sp. +++ *Escherichia coli* +++ ESBL *Escherichia coli* +++ *Klebsiella sp.* +++ ESBL *Klebsiella* sp. +++ *Serratia* sp. +++ *Enterobacter* sp. +++ *Bacteroides fragilis* +++ *Pseudomonas aeruginosa* ++ (except ertapenem) *Acinetobacter* sp. ++ (except ertapenem)	Intra-abdominal infections Febrile neutropenia (except ertapenem) Pneumonia, hospital-acquired or ventilator-associated (except ertapenem) Skin/skin structure infections, necrotizing (broad-spectrum coverage, except ertapenem) Urinary tract infections Osteomyelitis

+++, excellent activity; ++, good activity; +, some activity; MSSA, methicillin-susceptible *Staphylococcus aureus*; ESBL, extended spectrum β-lactamases; KPC, Klebsiella pneumoniae carbapenemase; MRSA, methicillin-resistant *Staphylococcus aureus*.

Table 3. Gram-positive antibiotic spectrum of activity and infectious diseases treated (23)

Antibiotic Class	Spectrum of Activity		Commonly Treated Infectious Diseases
	Gram-Positive	Gram-Negative	
Vancomycin	Streptococci +++ MSSA/MRSA +++ *Staphylococcus epidermidis* +++ *Enterococcus faecalis* +++ *Enterococcus faecium* +	No activity	Bloodstream infections Clostridium difficile colitis (oral) Endocarditis Osteomyelitis Pneumonia, hospital-acquired or ventilator-associated Sepsis and septic shock Skin/skin structure infections
Lipopeptides Daptomycin	See vancomycin, plus VRE, VISA/VRSA	No activity	Bloodstream infections Endocarditis Osteomyelitis
Oxazolidinones Linezolid Tedizolid	See vancomycin, plus VRE, VISA/VRSA		Enterococcal infections (VRE), including bacteremia (linezolid) Pneumonia, hospital-acquired or ventilator-associated (linezolid) Skin/skin structure infections
Lipoglycopeptides Telavancin Dalbavancin Oritavancin	See vancomycin, plus VRE, VISA/VRSA		Bloodstream infections, *Staphylococcus aureus* (telavancin) Pneumonia, hospital-acquired or ventilator-associated (telavancin) Skin/skin structure infections

+++, excellent activity; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*; +, some activity; VRE, vancomycin-resistant enterococci; VISA/VRSA, vancomycin-intermediate *Staphylococcus aureus*/ vancomycin-resistant *Staphylococcus aureus*.

been proposed as a way to increase antibiotic exposure and combat organisms with higher MICs (24).

In the 1980s, vancomycin dosing in patients on dialysis was recommended to be 15 mg/kg every 7–10 days, as virtually no drug was removed during dialysis sessions (25). With the emergence of high-flux dialysis filters, vancomycin clearance in dialysis has increased resulting in the typical thrice-weekly dosing schedule. In patients receiving vancomycin during the last hour of dialysis, higher intradialytic maintenance doses are needed to achieve predialysis trough concentrations of 15–20 μg/ml (27).

Nephrotoxicity is a common concern with vancomycin therapy, and is associated with concurrent nephrotoxin administration, (*e.g.*, gentamicin, piperacillin-tazobactam), targeting troughs 15–20 μg/ml, obesity, high daily doses, and extended duration of treatment (13). In general, appropriately dosed vancomycin in noncritically ill patients for the treatment of less serious infections has minimal risk of nephrotoxicity (13).

Lipopeptides

Daptomycin is the only member of the lipopeptide class of antibiotics. It exhibits concentration-dependent bactericidal activity against a variety of Gram-positive bacteria through depolarization of bacterial cell membranes, causing loss of membrane potential and subsequent cell death (23). Daptomycin is highly protein bound (86% in patients on hemodialysis) with a low volume of distribution, thus making it an ideal agent in the treatment of bloodstream infections (28). Importantly, daptomycin should be avoided in pulmonary infections as it is inactivated by pulmonary surfactant.

Daptomycin is primarily (78%) excreted in the urine as unchanged drug (23). Consequently, the $t_{1/2}$ of daptomycin is prolonged to 30 hours in patients receiving hemodialysis compared with 8 hours in patients with normal kidney function (28). Dose-adjustment of daptomycin to a 48-hour dosing interval is recommended for patients with a creatinine clearance <30 ml/min or requiring hemodialysis (28). However, this does not align with typical thrice-weekly hemodialysis schedules. To better achieve AUC:MIC targets, a 50% dose increase has been proposed during the 72-hour interdialytic period (29). Although this dose modification optimizes drug exposure, there is a subsequent increased probability of exceeding a 72-hour minimum concentration of 24.3 mg/L, which has been associated with an increased risk of daptomycin skeletal-muscle toxicity (29). In addition to a 30-minute infusion, daptomycin can be administered over 2 minutes, which may be useful to facilitate quicker patient turnaround in dialysis clinics (28,29).

A serious side effect of daptomycin therapy is myopathy. Because of this, patients should have creatine phosphokinase concentrations obtained weekly (even more frequently in patients with impaired kidney function) and be monitored for muscle pain or weakness during therapy (28). Concomitant administration of statins with daptomycin is not recommended; however, recent literature suggests that this combination was associated with numerically higher but not statistically significant rates of myopathy or creatine phosphokinase elevations, and that statin therapy, when

clinically necessary, should not impede daptomycin use in serious infections (30). Additional rare side effects of daptomycin include eosinophilic pneumonia and peripheral neuropathy. Of note, daptomycin exhibits a concentration-dependent drug-laboratory test interaction with recombinant thromboplastin, resulting in false prothrombin time prolongation and international normalized ratio elevation. This interaction may be minimized by collecting these laboratory values at trough plasma daptomycin concentrations (28).

Oxazolidinones

Until the release of tedizolid in 2014, linezolid was the sole agent in the oxazolidinone class. Targeting the P-site on the 50S ribosomal subunit, these bacteriostatic agents block bacterial protein synthesis (23). The oxazolidinones do not require dose adjustment for kidney dysfunction as the majority of both drugs undergo nonrenal clearance (31). Linezolid is metabolized *via* oxidation to two inactive metabolites, aminoethoxyacetic acid and hydroxyethyl glycine, that do accumulate in CKD with unknown clinical significance (32). Potential risks should be weighed against benefits when using linezolid in this patient population. Thirty percent of linezolid is removed *via* dialysis, so no dosage adjustments are needed; however, it is recommended that the second of the two daily doses be administered after dialysis (32).

Prolonged courses of linezolid have been associated with optic and peripheral neuropathies and myelosuppression. Tedizolid is not associated with these adverse effects, although long-term safety data in humans beyond 21 days is not available (31). Both agents weakly and reversibly inhibit monoamine oxidase-A and -B, thus caution is warranted with coadministration of serotonergic agents (31).

Lipoglycopeptides

First released in 2009, telavancin was the original member of the lipoglycopeptide class with dalbavancin and oritavancin receiving US Food and Drug Administration approval in 2014. These agents are structurally related to vancomycin and share a similar mechanism of action; however, they display increased potency because of their ability to dimerize and anchor themselves to bacterial cell walls *via* lipophilic side chains (33). Additionally telavancin and oritavancin disrupt membrane potential and permeability, resulting in cell lysis (33). Lipoglycopeptides are concentration-dependent bactericidal antibiotics, and antibacterial efficacy has been best correlated to AUC:MIC ratios (33).

Telavancin primarily undergoes elimination via the kidneys with 76% found in the urine as unchanged drug, thus dose adjustments are necessary when creatinine clearance falls below 50 ml/min (34). No dosing recommendations are formally provided in the product labeling for hemodialysis; however, every 48 hours or thrice-weekly dosing regimens were found to be effective in a small retrospective case series (35). At present, black box warnings are issued for telavancin regarding nephrotoxicity and increased mortality in patients with preexisting moderate/severe impaired kidney function (creatinine clearance <50 ml/min) who are being treated for hospital-acquired or ventilator-associated bacterial pneumonia (34). A *post hoc* analysis of the Assessment of Telavancin for Treatment of Hospital-Acquired Pneumonia (ATTAIN) trials suggests that the increased mortality in this patient population may have been related to a greater number of patients with Gram-negative organisms at baseline in the telavancin groups and by inadequate treatment of these Gram-negative organisms (36). Furthermore, in patients with severe kidney dysfunction or requiring hemodialysis, it has been demonstrated that telavancin's biologic activity against *S. aureus* is maintained (37). Caution is still warranted as not all differences in mortality seen in the ATTAIN trials can solely be attributed to Gram-negative infection in patients with creatinine clearance <50 ml/min. In clinical trials, telavancin had higher rates of nephrotoxicity compared with vancomycin, but the mechanism behind this is unknown (34).

Dalbavancin and oritavancin share similar pharmacokinetic features, with long $t_{1/2}$ and linear kinetic profiles. One third of dalbavancin is excreted in the urine as unchanged drug and a dose reduction is recommended in patients with creatinine clearance <30 ml/min. However, no dose adjustments are recommended in patients on dialysis as they share similar pharmacokinetics to patients with mild to moderate CKD (38). Oritavancin is not removed by hemodialysis and has not been studied in patients with creatinine clearance <30 ml/min or ESKD (39).

As oritavancin is a weak inhibitor of CYP2C9 and CYP2C19 and an inducer of CYP3A4 and CYP2D6, its coadministration with warfarin should be closely monitored because of increased drug exposure, as a 31% increase in the mean AUC of warfarin has been reported (39). Notably, both telavancin and oritavancin interfere with coagulation tests (prothrombin time, international normalized ratio, activated partial thromboplastin time, and activated clotting time), thus coadministration of either agent with unfractionated heparin is contraindicated (34,40).

Aminoglycoside Antibiotics

Aminoglycosides are a bactericidal class of antibiotics that exert their effects through inhibition of bacterial protein synthesis (41). Risks of oto- and nephrotoxicity has led clinicians to limit their use (42). However, aminoglycosides have retained activity against many multidrug resistant organisms (Table 4), and so still play an important role in antibiotic therapy today. They exhibit concentration-dependent pharmacodynamics, hence peak:MIC ratios of 10–12 (43) are most associated with antibacterial efficacy in Gram-negative infections (42). Traditionally the aminoglycosides are dosed by giving lower doses (*e.g.*, gentamicin doses of 3–6 mg/kg per day) (44,45) divided into two or three doses per day, with serum concentration monitoring to guide dose adjustments However, a more optimal method of dosing, called "high dose, extended interval," consolidates the doses into a larger daily dose (*e.g.*, gentamicin 7 mg/kg administered once daily) (5), to optimize the peak concentrations obtained. Because high residual concentrations are associated with nephrotoxicity, the dosing interval using this method is extended to 36 or 48 hours in patients with impaired kidney function to allow them to fully eliminate the drug. This high dose, extended interval dosing allows clinicians to maximize antibacterial efficacy as well as limit toxicities, as the intervals are extended long enough to allow

Table 4. Miscellaneous antibiotic spectrum of activity and infectious diseases treated (41,51)

Antibiotic Class	Spectrum of Activity		Commonly Treated Infectious Diseases
	Gram-Positive	Gram-Negative	
Aminoglycosides	Synergy only	Enterobacteriaceae ++	Endocarditis
Amikacin	*Enterococcus* sp.	*Pseudomonas aeruginosa* ++	Pneumonia, hospital-acquired or ventilator-associated
		Haemophilus influenzae +	
Gentamicin	MSSA	*Moraxella catarrhalis* +	Urinary tract infections
Tobramycin			Pyelonephritis
			Synergy (Gram-positive infections)
Fluoroquinolones	Streptococci +++ (L, M, D)	*Moraxella catarrhalis* +++ (except D)	Intra-abdominal infections
Ciprofloxacin (C)	MSSA/MRSA +++ (D)	*Haemophilus influenza* +++ (L, M)	Osteomyelitis (C)
Delafloxacin (D)	*Enterococcus faecalis* +++ (D)	*Escherichia coli* +++	Pneumonia, community-acquired (L, M)
Ofloxacin (O)		ESBL *Escherichia coli* +++	Pneumonia, hospital-acquired or ventilator-associated (C, L)
Levofloxacin (L)		*Klebsiella sp.* +++	Prostatitis (C, L)
Moxifloxacin (M)		*Proteus sp.* +++ (except D)	Urinary tract infections (except moxifloxacin)
		Serratia sp. +++ (except D)	Pyelonephritis (except M)
		Enterobacter sp. +++	Skin/skin structure infections (D)
		Citrobacter sp. +++ (except D)	Atypical coverage: *Legionella* sp., *Mycoplasma pneumoniae*, *Chlamydophila* sp.
		Pseudomonas aeruginosa ++ (except M)	Skin/soft tissue infections
		Bacteroides fragilis ++ (M)	Urinary tract infections
Sulfamethoxazole-trimethoprim	MSSA/MRSA +++	*Escherichia coli* ++	Pyelonephritis
	Staphylococcus epidermidis +++	ESBL *Escherichia coli* ++	*Pneumocystis* pneumonia
	Streptococcus pyogenes +++	*Klebsiella sp.* ++	Upper respiratory tract infections
	Streptococcus pneumoniae +	*Serratia* sp. ++	
		Proteus sp. ++	

++, good activity; MSSA, methicillin-sensitive *Staphylococcus aureus*; +, some activity; L, levofloxacin; M, moxifloxacin; D, delafloxacin; +++, excellent activity; C, ciprofloxacin; MRSA, methicillin-resistant *Staphylococcus aureus*; O, ofloxacin; ESBL, extended-spectrum β-lactamases.

the antibiotic elimination to concentrations ≤1 μg/ml (and in most cases to undetectable levels). This method of dosing takes advantage of the aminoglycosides ability to induce a "postantibiotic effect" (42). That is, they continue to exert antibacterial effects even when drug concentrations fall below the bacteria's MIC for a portion of the dosing interval.

Clinicians must be cautious when using this high dose, extended interval dosing in patients with creatinine clearance <30–40 ml/min as these patients are not able to remove aminoglycosides effectively. The high doses could potentially produce prolonged elevations in aminoglycoside concentrations, eventually leading to toxicities. For these patients, traditional dosing with close therapeutic monitoring is still recommended.

In patients on dialysis, aminoglycosides are commonly given after each dialysis session to prevent significant removal by hemodialysis (5). An interesting way to optimize the pharmacodynamics of aminoglycosides in dialysis would actually involve giving larger doses before hemodialysis to optimize antibacterial killing, and utilizing the increased clearance achieved by the hemodialysis process to reduce concentrations and prevent toxicity. The efficacy of this method of dosing needs to be further evaluated, but is worth future study and consideration, especially in patients receiving regular dialysis and struggling with life-threatening, multidrug-resistant, Gram-negative infections (46).

Fluoroquinolones

Fluoroquinolones have been widely prescribed in the United States since their initial release in the late 1980s because of their broad antimicrobial coverage, availability in an oral dosage form, and efficacy in a variety of infectious disease states. Currently, five fluoroquinolones are available in the United States market for systemic administration: ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin, and delafloxacin. These bactericidal agents target and inhibit DNA synthesis through inhibition of DNA gyrase in Gram-negative bacteria and topoisomerase IV in Gram-positive bacteria (47).

Fluoroquinolones have high oral bioavailability and excellent tissue penetration (47). Classically, these agents are categorized as having concentration-dependent pharmacodynamics. Interestingly, many fluoroquinolone pharmacodynamic studies report that the free (unbound drug) AUC:MIC ratio better correlates to clinical cure whereas the free peak:MIC ratio measures for the potential of bacterial resistance emergence (48). On the basis of their pharmacodynamic characteristics, the dosing interval should be lengthened, but the dose maintained. Except for moxifloxacin, fluoroquinolones are cleared by the kidneys and will need dose adjustments in patients with impaired kidney function (47).

Tendon rupture, peripheral neuropathy, and CNS effects are some of the serious adverse effects associated with fluoroquinolones that led the US Food and Drug Administration to issue a safety warning in 2016 recommending restrictions of their use in uncomplicated infections to situations where there are no alternate treatment options (49). In July 2018, classwide labeling changes were added to highlight the risk of mental health side effects and hypoglycemic coma (50).

In patients with CKD, an important but sometimes overlooked drug interaction occurs between phosphate binders and fluoroquinolones. Fluoroquinolones are known to chelate with di- and tri-valent cations, resulting in decreased antibiotic absorption and potentially treatment failure (5). In addition, caution is warranted when combining fluoroquinolones with other QT interval-prolonging medications such as antiemetics, antiarrhythmics, and antipsychotics (51).

Sulfamethoxazole-Trimethoprim

Sulfamethoxazole, like other sulfonamides, is a competitive inhibitor of dihydropteroate synthase, a bacterial enzyme involved in producing a precursor to folic acid (51). In the United States, sulfamethoxazole is only available in combination with trimethoprim, an antibiotic that inhibits dihydrofolate reductase, a downstream enzyme also involved in the production of folic acid. Trimethoprim is 20–100 times more potent than sulfamethoxazole, and so to achieve pharmacodynamic targets and maximize effectiveness, sulfamethoxazole concentrations should be 20 times the trimethoprim concentration (51).

The $t_{1/2}$ of sulfamethoxazole and trimethoprim in individuals with normal kidney function range from 9 to 11 and 10 to 15 hours, respectively. These $t_{1/2}$ become prolonged in kidney disease, with $t_{1/2}$ of 20–50 hours and 24 hours, respectively in ESKD (52–54). One of sulfamethoxazole's metabolites, N4-acetyl-sulfamethoxazole, is primarily excreted by the kidney and may accumulate in patients with uremia, although the significance of this remains unknown (53).

The dose of sulfamethoxazole-trimethoprim should be reduced in patients with creatinine clearance <30 ml/min (54). Hemodialysis is moderately effective in the elimination of both drugs, which results in a reduction of their $t_{1/2}$ toward normal values during the hemodialysis session (54,55).

Sulfamethoxazole-trimethoprim is generally a safe medication with well defined adverse effects. Gastrointestinal upset is reported in 3%–8% of patients. Hematologic side effects are less common, but include megaloblastic anemia, leukopenia (particularly in immunocompromised patients), and thrombocytopenia (54,56). Trimethoprim is associated with hyperkalemia, as it inhibits amiloride-sensitive sodium channels in the distal nephron in a dose-related manner. This was thought to be most likely to occur in patients receiving high doses, but hyperkalemia can occur with standard doses of the medication, particularly in those with impaired kidney function (57).

Controversy surrounds the nephrotoxic potential of sulfamethoxazole-trimethoprim in patients with CKD (10). Some authors have reported a deterioration of kidney function in patients taking the antibiotic (58,59), whereas others have failed to confirm the association (60). Nephrotoxicity appears to be due to the sulfonamide component, which can cause hypersensitivity interstitial nephritis, tubular necrosis, or crystalluria (10). It should also be noted that trimethoprim reduces the tubular secretion of creatinine, which can cause an increase in serum creatinine without any true change in GFR (10).

Antibiotic prescribing is difficult, particularly in patients with kidney disease. However, knowledge of a drug's pharmacology, place in therapy, and pharmacokinetic and

pharmacodynamic consideration can aid the clinician in optimizing antibiotic use to maximize efficacy and minimize adverse effects in patients. Resources and guidelines do exist to aid in dose optimization (61–63), although the recommendations are not consistent or applicable in all clinical situations (*e.g.*, AKI, different modalities of kidney replacement therapies) (4,64). A list of resources for dosing medications in patients with CKD has been included in Supplemental Table 1. When consulting the literature for dosing recommendations, it is important to select more recent studies utilizing similar dialysis technologies, as pharmacodynamic optimization strategies and dialysis technologies continue to evolve. However, a working knowledge of antibiotic pharmacology can aid the clinician in making thoughtful prescribing decisions designed to maximize efficacy and limit adverse effects in a particularly vulnerable population.

Disclosures

None.

Supplemental Material

This article contains the following supplemental material online at http://cjasn.asnjournals.org/lookup/suppl/doi:10.2215/CJN.08140718/-/DCSupplemental.

Supplemental Table 1. Resources for dose adjustments in CKD.

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Nephropharmacology
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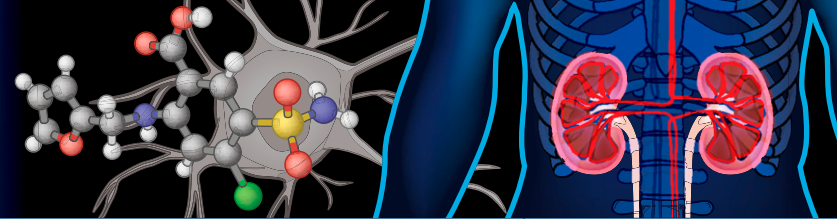

Clinical Pharmacology in Diuretic Use

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Diuretics are among the most commonly prescribed drugs and, although effective, they are often used to treat patients at substantial risk for complications, making it especially important to understand and appreciate their pharmacokinetics and pharmacodynamics (see recent review by Keller and Hann [1]). Although the available diuretic drugs possess distinctive pharmacokinetic and pharmacodynamic properties that affect both response and potential for adverse effects, many clinicians use them in a stereotyped manner, reducing effectiveness and potentially increasing side effects (common diuretic side effects are listed in Table 1). Diuretics have many uses, but this review will focus on diuretics to treat extracellular fluid (ECF) volume expansion and edema; the reader is referred elsewhere for discussion of diuretic treatment of hypertension, kidney stones, and other conditions.

Classification and Mechanisms of Action

Diuretic drugs are typically classified first according to their predominant site of action along the nephron and second by the mechanism by which they inhibit transport (Figure 1A). The loop diuretics furosemide, bumetanide, and torsemide act from the lumen to inhibit the Na-K-2Cl cotransporter (NKCC2, encoded by *SLC12A1*) along the thick ascending limb and macula densa. As organic anions, they bind within the translocation pocket on the transport protein by interacting with the chloride-binding site (2) (Figure 1B, see below for clinical relevance). Because they are larger than chloride, they are not transported through the pocket, and thereby inhibit the transporter. Distal convoluted tubule diuretics (thiazides and thiazide-like drugs) are also organic anions that act in much the same manner, but bind to the thiazide-sensitive NaCl cotransporter (NCC, encoded by *SLC12A3*) along the distal convoluted tubule (Figure 1A). This mechanism of action accounts for a key aspect of loop and distal convoluted tubule diuretic action; these drugs both exert their effect from the luminal side of the tubule.

Potassium-sparing diuretics include drugs that block apical sodium channels (amiloride and triamterene) and those that antagonize mineralocorticoid receptors (spironolactone and eplerenone). A new nonsteroidal mineralocorticoid blocker, finerenone, is currently in phase 3 clinical trials. The mineralocorticoid blockers and perhaps ethacrynic acid, a more toxic loop diuretic, act within cells and do not require secretion into the tubule lumen.

Gastrointestinal Absorption of Diuretics

The normal metabolism of loop diuretics is shown in Figure 2A. Furosemide, bumetanide, and torsemide are absorbed relatively quickly after oral administration (see Figure 2B), reaching peak concentrations within 0.5–2 hours (3,4); when administered intravenously, their effects are nearly instantaneous. The oral bioavailability of bumetanide and torsemide typically exceeds 80%, whereas that of furosemide is substantially lower, at approximately 50% (see Table 2) (5). Although the $t_{1/2}$ of furosemide is short, its duration of action is longer when administered orally, as its gastrointestinal absorption may be slower than its elimination $t_{1/2}$. This is a phenomenon called "absorption-limited kinetics" (3) and may explain the mnemonic that this drug "lasts 6 hours" (6). This is not the case for bumetanide and torsemide, where oral absorption is rapid (7). On the basis of oral bioavailability, when a patient is switched from intravenous to oral loop diuretic, the dose of bumetanide or torsemide should be maintained, whereas the dose of furosemide should be doubled (7); in practice, however, and as discussed further below, other factors affect diuretic efficacy, and a fixed intravenous/oral conversion cannot be given (8).

The loop diuretics have steep dose-response curves. This property, although typically taught to students and residents, is often neglected in clinical practice but is crucial to optimal use. Figure 2C shows a typical natriuretic response plotted versus the logarithm of the plasma diuretic concentration. Inspection reveals that there is little diuretic or natriuretic effect below a given plasma concentration (identified as the "threshold"), above which the response increases rapidly. Although such relations are typically plotted as the logarithm of the diuretic concentration or dose, clinicians do not typically "think" in logarithmic terms. This underlies the reasoning behind the common recommendation to "double the dose," if no response is obtained. At higher concentrations, a plateau or "ceiling" is reached, with progressively higher plasma concentrations failing to elicit more natriuresis. Although this fact has been used to invoke the concept of ceiling doses of loop diuretics, we will argue that increasing a diuretic dose above this ceiling often elicits more natriuresis, owing to pharmacokinetic considerations (see below).

As should be evident from Figure 2C, a diuretic dose must exceed the threshold to be effective; yet the failure to give a dose that exceeds the threshold is one

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Table 1. Common side effects of diuretics

Loop diuretics
Hypersensitivity reactions
Extracellular fluid volume depletion
Hypokalemic alkalosis
Hypomagnesemia
Ototoxicity
Distal convoluted tubule diuretics
Hypersensitivity reactions
Hyponatremia
Hypokalemic alkalosis
hyperglycemia/diabetes
Hyperuricemia/gout
Hypomagnesemia
Hypokalemia and prerenal azotemia, when combined with loop diuretics
Potassium-sparing diuretics
Hypersensitivity
Hyperkalemia
Metabolic acidosis
Azotemia
Gynecomastia, vaginal bleeding (spironolactone)

of the most common errors in diuretic usage. The problem is that the threshold is not easily estimated in an individual, especially an individual with kidney or heart disease. Although nearly all healthy individuals will respond to 20 mg furosemide (or its equivalent), given orally, healthy individuals are not typically treated. As discussed below, conditions that predispose to ECF volume expansion and edema alter both the pharmacokinetics and pharmacodynamics of diuretics. It is little wonder that an empirically selected dose may be ineffective. Below, we will provide broad generalizations about dose adjustments for individuals with a variety of edematous disorders. Yet, adherence to algorithms may lead to diuretic failure. Instead, it is often best to approach a patient as an "*n* of one trial," that is, start with a dose consistent with the clinical guidelines (more aggressive for acute edema, more conservative for more chronic processes) and then adjust the dose according to the response.

Although limited bioavailability is a concern with furosemide, a larger problem may be its inconsistent bioavailability. Furosemide absorption varies from day to day in an individual, and between individuals (9,10). Absorption is also affected by food consumption, unlike that of bumetanide or torsemide (11,12), although the clinical significance of this effect has been doubted (3). The more consistent bioavailability of torsemide, compared with furosemide, and its relatively longer $t_{1/2}$, have suggested that it may be a superior loop diuretic, as suggested by two small, clinical trials (13–16). A recent *post hoc* analysis of the large Effect of Nesiritide in Patients with Acute Decompensated Heart Failure study suggested that patients with heart failure discharged on torsemide might have lower mortality (17). Yet, none of these studies is sufficiently powered or rigorous enough to be considered definitive, and some other studies do not suggest such a benefit (18).

Gastrointestinal absorption can be slowed, especially during exacerbations of edematous disorders such as heart failure, although again, this may be true primarily of furosemide (19). Although total bioavailability is typically maintained in these situations, natriuresis may be impaired when absorption is slowed, especially given a concomitant increase in natriuretic threshold, as shown in Figure 2B. As an example, the areas under the curves for arbitrary intravenous and doubled oral furosemide doses may be similar, but the time above the

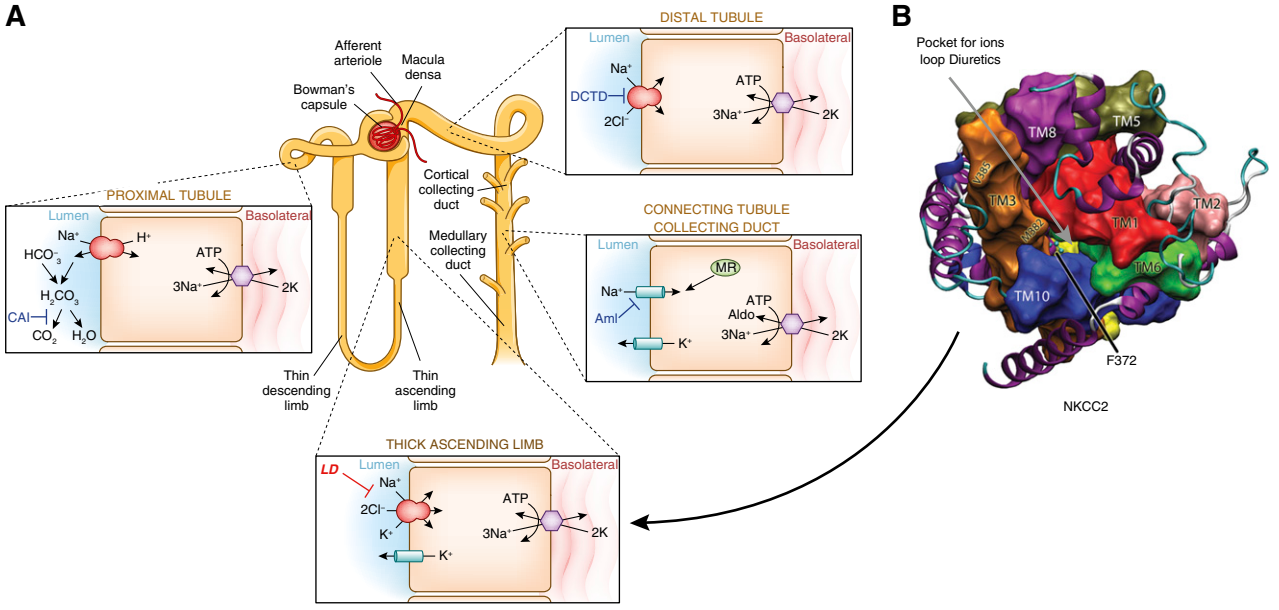

Figure 1. | Sites of sodium reabsorption and diuretic action along the nephron. (A) Nephron figure showing percentages of sodium reabsorption by associated segment. (B) Homology structural model of the loop diuretic–sensitive NKCC2 viewed from the extracellular surface. The pocket for ion translocation and diuretic binding is shown by the arrow. Mutation of a key phenylalanine (F372) alters diuretic binding (reconstruction adapted from Somasekharan *et al.* [2]). Aldo, aldosterone; Aml, amiloride (and triamterene); CAI, carbonic anhydrase inhibitors; DCTD, distal convoluted tubule diuretic; LD, loop diuretics; MR, mineralocorticoid receptor, site of spironolactone and eplerenone action (not shown).

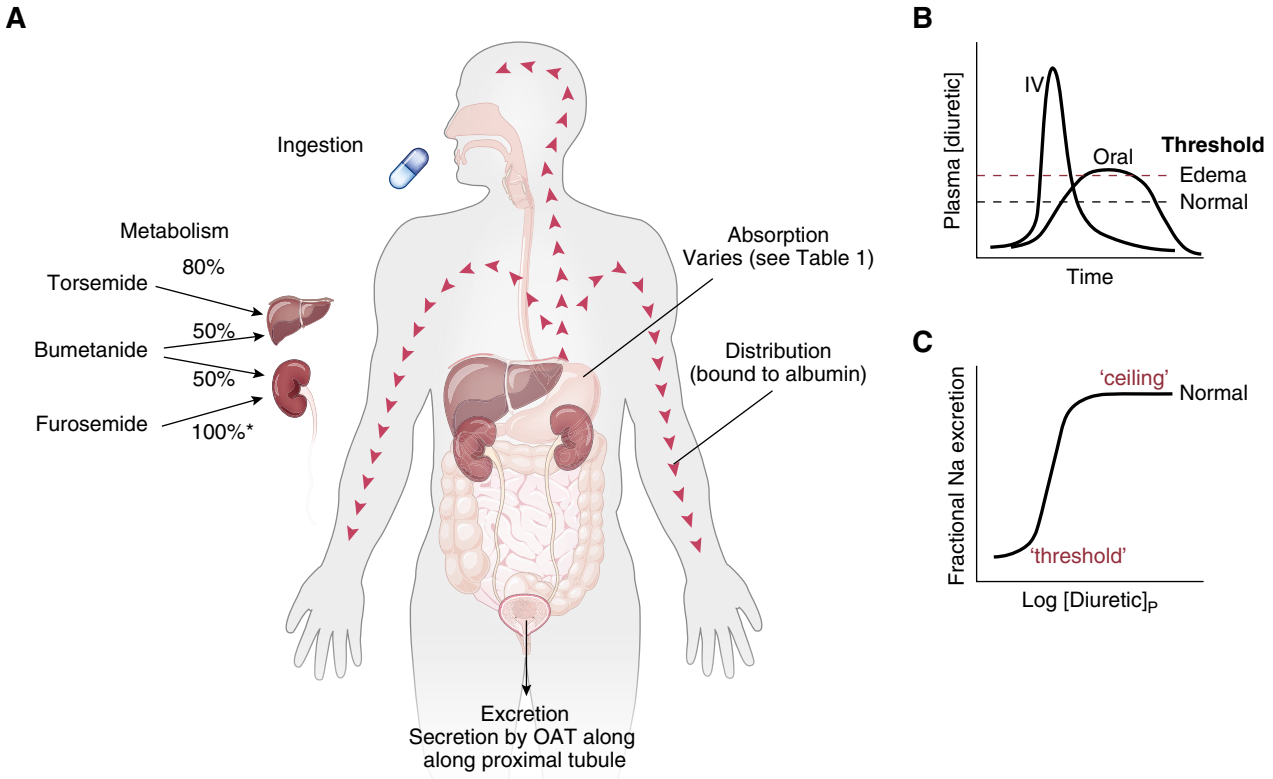

Figure 2. | **(A) Features of absorption, distribution, metabolism, and excretion (so-called ADME) of drugs.** (B) Comparing the plasma diuretic concentration as a function of time after oral or intravenous diuretic administration. The dashed lines show natriuretic thresholds in normal individuals and in those with edema. Note that the primary determinant of natriuresis is the time above the threshold, indicating why route of administration has different effects in stable patients and in those with severe edema. In a normal individual, an oral dose may be effective, whereas it may not be in edema despite retained bioavailability. (C) Classic dose-response curve, plotted versus the logarithm of the plasma concentration. Note the threshold for natriuresis and the maximal level, often called the ceiling. IV, intravenous.

natriuretic threshold may be different when the natriuretic threshold is increased by disease. This is likely to explain the common observation that intravenous doses of loop diuretics, which achieve higher peak levels, may be effective when oral doses lose their effectiveness, especially if the natriuretic threshold is increased.

Volumes of Distribution, Metabolism, and $t_{1/2}$

Loop diuretics are organic anions that circulate tightly bound to albumin (>95%). Thus, their volumes of distribution are low, except during extreme hypoalbuminemia (20). This has suggested that severe hypoalbuminemia might impair diuretic effectiveness, owing to impaired delivery to

Table 2. Pharmacokinetics of commonly used diuretics

Diuretic	Oral Bioavailability, %	Elimination $t_{1/2}$, h			
		Normal	CKD	Cirrhotic Ascites	Heart Failure
Furosemide	50 (10–100)	1.5–2	2.8	2.5	2.7
Bumetanide	80–100	1	1.6	2.3	1.3
Torsemide	68–100	3–4	4–5	8	6
Hydrochlorothiazide	55–77	6–15	Prolonged		
Chlorthalidone	61–72	40–60	Prolonged		
Metolazone	70–90[a]	14–20	Prolonged		
Amiloride	~50[b]	6–26	100[d]	Not changed	
Spironolactone	>90	1.5[c]			

Data are presented as single reported values or range of reported values. Values for furosemide are given as the mean (range). When precise values were not provided, descriptive terms are provided.
[a]Absorption may be decreased in heart failure.
[b]Decreased by food.
[c]Active metabolites of spironolactone have $t_{1/2}$ of >15 hours.
[d]Active metabolites accumulate in CKD. Adapted from Karin (82).

the kidney, and that albumin administration might enhance natriuresis. This conjecture was supported in an early proof-of-concept study (20), but subsequent larger studies have produced mixed results. A relatively recent meta-analysis concluded that the existing data, albeit of poor quality, suggest transient effects of modest clinical significance for coadministration of albumin with furosemide in hypoalbuminemic patients (21). A similar assessment is reflected in the Kidney Disease Improving Global Outcomes guidelines for diuretic treatment of GN (22). Nevertheless, most recent studies have enrolled patients whose serum albumin concentrations exceeded 2 g/dl, so that these considerations may not apply for severely hypoalbuminemic patients. Some guidelines continue to suggest that albumin infusion should be used as an adjunct to diuretics when nephrotic patients appear to have vascular volume depletion (or appear to be "underfilled") (23).

Approximately 50% of an administered furosemide dose is excreted unchanged into the urine. The remainder appears to be eliminated by glucuronidation, predominantly also in the kidney. Torsemide and bumetanide are eliminated both by hepatic processes and urinary excretion, although hepatic metabolism may predominate, especially for torsemide (24). The differences in metabolic fate mean that the $t_{1/2}$ of furosemide is prolonged in kidney failure, where both excretion by the kidney and kidney-mediated glucuronidation are slowed. In contrast, the $t_{1/2}$ of torsemide and bumetanide tend to be preserved in CKD (25). Although the ratio of equipotent doses of furosemide-to-bumetanide is 40:1 in normal individuals, that ratio declines as kidney disfunction progresses (26). Although this apparent increase in furosemide potency may seem beneficial, it also likely increases the toxic potential of furosemide in the setting of AKI. Deafness and tinnitus from loop diuretics appear to result primarily from high serum concentrations, which inhibit an Na-K-2Cl isoform (NKCC1, encoded by *SLC12A2*). This transport protein, which is different from that expressed along the thick ascending limb, is expressed by the stria vascularis and participates in secretion of potassium-rich endolymph (27,28). This complication was seen more frequently in the past when very large bolus doses of loop diuretics were used to forestall dialysis (29). In one meta-analysis of furosemide use for patients with AKI, the odds ratio for hearing loss was more than three when high-dose furosemide was used; it should be noted, however, that the doses cited in that analysis (1–3 g daily) exceeded those currently recommended (30). The tendency of bolus infusion to lead to high peak furosemide concentrations is one reason that many investigators recommend continuous infusions instead (1).

Loop diuretics exert their actions by binding to transport proteins along the luminal membrane of thick ascending limb cells. To gain access to the tubular fluid and therefore to their sites of activity, they must be secreted across the proximal tubule, as their protein binding in plasma largely prevents glomerular filtration. Although some data suggest that bumetanide is also delivered into the tubule lumen by filtration (31), a preponderance of evidence suggests that it also gains entry primarily via secretion (32). Peritubular uptake is mediated by the organic anion transporters OAT1 and OAT3, whereas the apically located multidrug resistance-associated protein 4 (Mrp-4) appears to mediate at least a portion of secretion into the tubular fluid. Mice lacking OAT1, OAT3, or Mrp-4 are resistant to loop and thiazide diuretics, illustrating the functional importance of these proteins (31,33).

Although human mutations in OAT1 have not been described, these pathways may be inhibited by drugs and endogenous toxins, thereby causing diuretic resistance (31). Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit diuretic secretion and alter diuretic responsiveness, and because of their frequent use, are an important cause of heart failure exacerbations (34). Yet other classes of drugs, including antihypertensives, antibiotics, and antivirals, may also interact with these transporters and cause resistance (35). Endogenous metabolites also compete for diuretic secretion, including indoxyl sulfate, carboxymethyl-propyl-furanpropionate, *p*-cresol sulfate, and kynurenate, which accumulate in CKD (36). In all of these situations, the natriuretic dose-response curve is shifted to the right (Figure 3A).

There are additional reasons that CKD is a loop diuretic–resistant state. Metabolic acidosis, which is frequently observed in uremia, depolarizes the membrane potential of proximal tubule cells (37), which also decreases organic anion secretion, an effect that may explain why diuretic secretion is enhanced by alkalosis (38). In addition to a shift in the dose-response curve, patients with CKD and those taking NSAIDs have a downward shift of the ceiling natriuresis, when expressed as absolute sodium excretion (rather than fractional). The mechanism for resistance attributable to NSAIDs is complex. Loop diuretic inhibition of NaCl reabsorption at the macula densa stimulates both renin secretion and prostaglandin (PG) production, the latter predominantly *via* cyclooxygenase-2 (39). When this happens, PG E2 feeds back on tubules, contributing to the resulting natriuresis by inhibiting NaCl transport along the thick ascending limb and collecting duct (40,41). NSAIDs block this PG-mediated antinatriuresis. When used chronically, NSAIDs increase the abundance and activity of NKCC2 along the thick ascending limb (42). Additionally, loop diuretics inhibit the second transporter isoform, NKCC1, mentioned above, which is also expressed by vascular smooth muscle cells; loop diuretics contribute to afferent arteriolar vasodilation by blocking this transporter (43), thus helping to maintain GFR despite a lower ECF volume. Again, this compensatory adaptation is largely dependent on PG production and can be blocked by NSAIDs. The clinical consequence of these effects is evident in the association between recent use of NSAIDs and risk for hospitalization in patients with heart failure (34). In fact, the combination of three classes of drugs that affect hemodynamics of the kidney, loop diuretics, angiotensin-converting inhibitors (or receptor blockers), and NSAIDs, is associated with AKI (44).

CKD also impairs the natriuretic response to diuretics through a different mechanism. It is frequently noted that the maximal natriuretic capacity of loop diuretics is maintained in the face of CKD, when natriuresis is measured as a fraction of filtered load (Figure 3A). Yet the maximal natriuretic effect of these diuretics, when measured as the more clinically relevant absolute rate, is markedly reduced (Figure 3B). This is because, as GFR and filtered sodium load decrease, kidneys suppress sodium

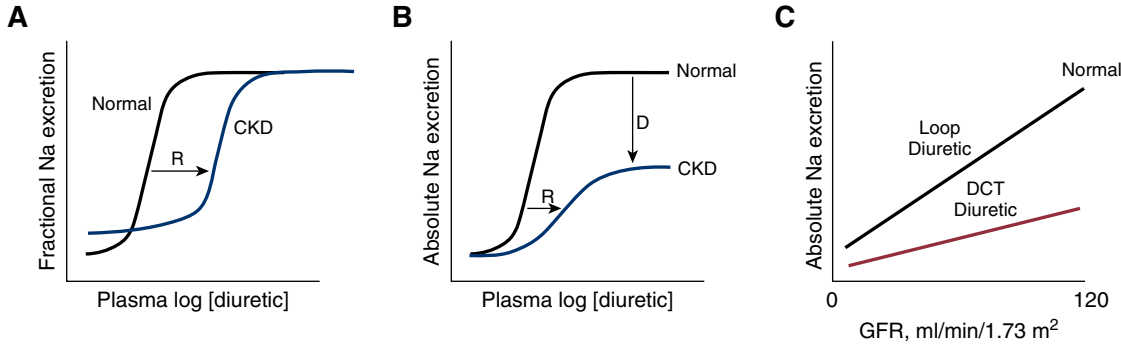

Figure 3. | **Pharmacokinetics and pharmacodynamics of diuretic action.** (A) Effects of CKD on diuretic actions. Note that in CKD, baseline fractional sodium excretion is high, to maintain absolute rates of sodium excretion equal to intake. There is a shift in the dose-response curve to the right (R), primarily owing to impaired diuretic secretion, but no change in the ceiling effect. (B) The same relationship plotted versus absolute rates of sodium excretion. The same rightward shift is evident, but the ceiling is lower, owing to the GFR reduction (as indicated by D). (C) Comparing effects of loop diuretics and distal convoluted tubule (DCT) diuretics on absolute sodium excretion, given a retained effect on fractional excretion.

reabsorption by the tubule to maintain the balance between dietary salt intake and urinary salt excretion. This suppression occurs along the thick ascending limb, so that even when a diuretic reaches the segment and inhibits the transporter, its net effect is reduced. Thus, NSAIDs and CKD cause diuretic resistance both by shifting the diuretic dose-response curve to the right (which can be overcome by higher doses) and by reducing maximal natriuresis (which cannot; compare Figure 3, A and B). This phenomenon likely explains the reduced effectiveness of distal convoluted tubule diuretics in CKD. If, like loop diuretics, maximal fractional sodium excretion remains constant as GFR declines, then their already modest ceiling will appear minimal when GFR is low (Figure 3C).

Loop diuretics are characterized by relatively short $t_{1/2}$ (see Table 2). Thus, the initial natriuresis typically wanes within 3–6 hours, so that a single daily dose leaves some 16–21 hours for the kidneys to compensate for salt and water losses. For individuals in steady state, the phenomenon of "postdiuretic NaCl retention" defines that fact that urinary NaCl excretion declines below the baseline when the diuretic effect wears off. This is typically true until another dose of diuretic is administered (45). It should be noted, however, that although this relationship applies to patients who are at steady state (and thereby excreting their daily intake of salt), it is altered in patients with decompensated edema, who may present during a period of positive NaCl balance, with urinary [NaCl] very low, even without diuretic administration. In this case, any increase in urinary NaCl excretion will be beneficial.

Regardless of these differences, the net NaCl loss from a diuretic typically results from a short period of natriuresis and a longer period of antinatriuresis. This accounts for the usual recommendation to use loop diuretics twice daily; clearly, from inspection of the $t_{1/2}$, this imperative is most important when using bumetanide and least so with torsemide. As noted above, when CKD progresses, the $t_{1/2}$ of furosemide is prolonged, increasing its apparent relative potency versus bumetanide. Even when administered twice daily, however, long internatriuretic periods limit drug efficacy; this is most important when dietary NaCl intake is high, as NaCl retention by the kidneys will lead to more positive NaCl balance.

One strategy to address $t_{1/2}$ issues, at least for hospitalized patients, is to infuse loop diuretics continuously. Although the advantages of this approach over high-dose bolus treatment remain largely speculative (46), the physiologic basis for this approach is appealing, and recent stepped care guidelines (see below) recommend continuous infusions (47). Along these lines, an investigational extended release formulation of torsemide that delivers torsemide to the circulation over 8–12 hours was reported recently to double salt and water losses in normal volunteers after a single dose, without increasing potassium excretion (48). If such a formulation, which should avoid some of the obvious pharmacokinetic limitations of short acting loop diuretics, works as well in patients with heart failure or nephrotic syndrome, it may change the standard approach to treatment.

Somewhat different considerations apply to patients with cirrhotic ascites. Here, relative gastrointestinal absorption tends to be preserved (49). Coupled with the tendency for relative underfilling in this setting, it is typically recommended to avoid intravenous diuretics, if possible (50). In this situation, a combination of furosemide with spironolactone, in a ratio of 40 mg furosemide to 100 mg spironolactone, is recommended in most patients, to balance efficacy and safety, although in patients with concomitant kidney disease, this ratio may need to be adjusted, with the goal of maintaining normokalemia (51).

Using Diuretics Effectively to Treat ECF Volume Expansion

When diuretics are initiated to treat edema, whether in a patient with normal or abnormal kidney function, it is essential to confirm that the dose provides a tubule concentration that exceeds the threshold (Figure 1B). That this threshold has been reached can be detected by moss ambulatory patients, who should notice an increase in urine volume within 2–4 hours of an oral dose. A discrepancy between diuresis and weight loss in outpatients

suggests that excessive NaCl consumption is limiting effectiveness; in this case, measuring 24-hour urine sodium excretion, using creatinine to confirm collection adequacy, may confirm excessive NaCl intake, although single urine [Na^+] collections may not give fully accurate results (52). For hospitalized patients, a dose reaching the threshold should lead to an increase in urine volume during the 6 hours that follow a dose. On the basis of the relationship of plasma diuretic concentration and time shown in Figure 2B, diuresis should occur more promptly after an intravenous dose. This difference may be especially pronounced if furosemide is the diuretic chosen. If an effect is not observed during this period, it is customary to double the dose, for example from 20 to 40 mg of furosemide or from 80 to 160 mg of furosemide, a recommendation predicated on the dose-response curve shown in Figure 2C. The dose is then escalated to a maximal safe level, as discussed below. Although loop diuretics are typically administered twice daily, there is no reason to introduce a second daily dose if the first dose does not exceed the threshold. Once a threshold has been reached, however, most patients will require two daily doses.

Although dose recommendations for loop diuretics have been published, on the basis of pharmacokinetic and pharmacodynamic considerations (24) or expert consensus (53), several more specific dose ranges have been tested in clinical trials. For acute decompensated heart failure, Felker and colleagues compared doses 2.5-times the home daily dose with one-times the home daily dose, given intravenously. Although differences in the primary outcome were not observed using the higher dose in this trial, prespecified secondary outcomes were encouraging, and negative consequences were not observed. Importantly, this and other recent trials, including those for patients with cardiorenal syndrome, aimed for 3–5 L of diuresis per day for initial treatment (47), rates that are more aggressive than often targeted. These studies emphasize that, for hospitalized patients, an aggressive approach to diuresis is often safe as well as effective. Prior concerns that diuretic drugs might be harmful to the kidney or the system overall, therefore, likely reflected confounding by indication when determined in observational trials (54). In fact, *post hoc* analyses of large trials suggest that those who experience a moderate increase in creatinine (worsening kidney function) may actually have better prognosis than those who do not (55,56).

The net or therapeutic natriuretic response to a diuretic is determined by the difference between the net sodium excreted in the urine and the sodium consumed. Although increasing a diuretic dose above the ceiling does not increase the maximal minute-natriuresis (the maximal rate of NaCl excretion per given time, see Figure 2C), it often increases the net natriuresis by prolonging the period during which the diuretic concentration exceeds the threshold (see Figure 2A). This is one reason that current guidelines for heart failure may recommend doses that exceed ceiling doses and are multiples of prior or home doses (see below and Ellison and Felker [45]).

In both normal individuals and in patients with ECF volume expansion, there is a linear relationship between ECF volume and sodium excretion ($U_{Na}V$), elegantly elucidated by Walser (57). This is similar to, but distinct from, the pressure natriuresis, which describes the relationship between mean arterial pressure and $U_{Na}V$. Diuretics are recommended universally to treat symptomatic ECF volume expansion, with rare exceptions, and therapeutic success is considered to be reduction in ECF. This invariably requires initial sodium and water losses, induced by diuretic doses that exceed the threshold (Figure 4). Yet the situation changes as initial treatment moves toward successful chronic treatment. At any therapeutically active dose, natriuresis wanes as ECF declines, an effect often called the "braking phenomenon" (58). This means that, at steady state, the individual returns to NaCl balance, during which urinary NaCl excretion is equal to dietary NaCl intake once again. This occurs, however, at a lower ECF volume than before treatment. Functionally, then, chronic diuretic treatment shifts the relationship between ECF volume and $U_{Na}V$ to the left (see Figure 4), thereby permitting NaCl excretion rates to again equal intake, albeit with lower ECF volume. It should be noted, however, that although daily NaCl excretion normalizes, the pattern of salt and water loss remains more episodic, so that a patient may complain that the diuretic regimen is increasing urine output.

Although the braking phenomenon is adaptive once ECF volume has been reduced successfully, it is maladaptive, when it occurs in the setting of persistent ECF volume expansion. Many factors resulting primarily from changes in ECF volume, such as stimulation of nerves innervating the kidney and activation of the renin-angiotensin system, likely contribute to braking (59,60), but it is now recognized that adaptive changes in segments other than the thick ascending limb also play an important role (61,62). Remodeling of the distal nephron occurs (63), leading to hypertrophy and hyperplasia, especially of distal segments. This results from increased salt delivery (64), increased angiotensin II (65) and aldosterone concentrations (66), and changes in potassium balance. The consequences of remodeling are that distal tubules increase their transport capacity to rival that of thick ascending limbs; for this reason, more of the NaCl that escapes the loop of Henle is reabsorbed distally, and net natriuresis is reduced.

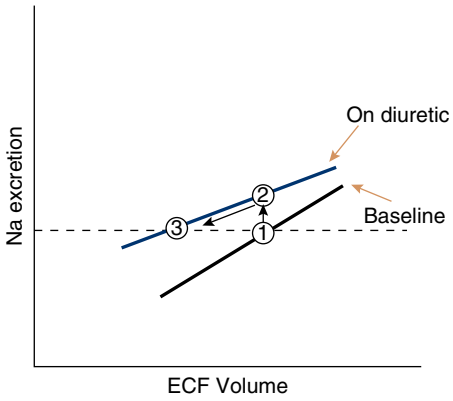

Figure 4. | Relationship between ECF volume and sodium excretion, based on (57)**.** Diuretics shift this curve upward (blue line), but may make it shallower. The baseline sodium excretion rate (which equals intake) is shown by the dashed line. After a diuretic is started, urinary sodium excretion rises by shifting to a new curve (from point 1 to point 2). Gradually (through the braking phenomenon) urinary sodium excretion declines back to the baseline level, but at a new and reduced ECF volume (from point 2 to point 3).

Adding a thiazide or thiazide-like drug will help to treat, and may even prevent, this type of adaptation and restore diuretic efficacy. Most commonly, especially in patients with CKD, metolazone is chosen as the second agent, although other thiazides may be equally effective (67). Interestingly, at least three factors may contribute to these beneficial effects. First, by blocking transport along the distal tubule, a site exhibiting transport activation, the potency of these normally weak diuretics will be increased (68). Second, when oral metolazone or chlorthalidone is used in this situation, its longer $t_{1/2}$ (approximately 14 and 50 hours [69]) means that postdiuretic NaCl retention may be attenuated. Third, these drugs may mitigate distal nephron remodeling and activation of the thiazide-sensitive NCC (70). Nevertheless, a key hazard of this approach is the substantial potential for hypokalemia (71). As hypokalemia is now recognized as the dominant factor activating NCC (72), such secondary effects counteract the goal of adding a second class of diuretic. In this situation, lower or less frequent doses may gain the benefits as well as limit the risks.

Table 3. Stepped pharmacologic care algorithm for heart failure

Level	Current Daily Furosemide Dose[a], mg	Bolus	Infusion Rate, mg/h	Metolazone (Oral)
1	≤80	40	5	0
2	81–160	80	10	5 mg daily
3	161–240	80	20	5 mg twice daily
4	≥240	80	30	5 mg twice daily

[a]Diuretic equivalents: 40 mg furosemide is considered equivalent to 1 mg bumetanide 20 mg torsemide. Adapted from Grodin *et al.* (47) and Bart *et al.* (73). The full algorithm provided in the references includes additional considerations for vasodilator, inotropic, or mechanical therapy for patients who fail to respond within 48 h.

Evidence-Based Diuretic Dosing for ECF Volume Expansion

Although recommendations for loop diuretic dosing have traditionally been made on the basis of pharmacological properties, some more recent studies of acute decompensated heart failure have focused on patient-centered outcomes. The Diuretic Strategies in Patients with Acute Decompensated Heart Failure trial compared high and low doses of loop diuretics for acute decompensated heart failure and showed that the higher dose (2.5 times the home daily dose) is well tolerated and effective. One concern about aggressive diuretic approaches in this situation is worsening kidney function, which was used as a harm signal in this study. Yet worsening kidney function in this trial, as indicated by a rise in creatinine, is actually associated with better, rather than worse, prognosis (55). When adequate diuresis does not occur, a stepped care approach, shown in Table 3, has been recommended (47). Although not compared directly with other approaches, this algorithm was used successfully in randomized trials and proved at least as effective as invasive techniques, such as ultrafiltration (73).

More limited but compelling data suggest that patients with cirrhotic ascites are best treated with a combination of furosemide and spironolactone, at a ratio of 40:100 mg (74). This preserves the plasma potassium concentration in most patients, although it may need to be adjusted if abnormalities occur. For patients with nephrotic syndrome, diuretic binding was previously suggested to contribute to resistance. Yet a study comparing the natriuretic effect of loop diuretics with and without protein displacement indicated clearly that this factor was not contributing (75). Another contributor in this situation is the cleavage of the epithelial sodium channel by filtered proteases (76); recent animal data suggest that this may be a target for intervention, with either protease inhibitors or amiloride (77).

Diuretics for AKI

Recommendations for and against diuretic use in AKI have varied widely. At the end of the 20th century, extremely high diuretic doses were often used, which can convert oliguric to nonoliguric AKI, but were found to be associated with deafness and no change in mortality in controlled trials (78). A later retrospective trial suggested that diuretic use in patients with AKI is associated with increased mortality, and suggested that "the widespread use of diuretics in critically ill patients with acute renal failure should be discouraged" (79). Yet, statistical approaches cannot overcome the inherent limitations in such retrospective studies. To address this concern and reduce confounding by indication, Grams *et al.* performed a *post hoc* analysis of data for patients with AKI from the Fluid and Catheter Treatment Trial (80). In this trial, patients with adult respiratory distress syndrome were randomized to liberal or restrictive fluid policies; for those randomized to restricted fluid, diuretics were used aggressively. The results of this trial suggested that patients who developed AKI who were randomized to a strategy that involved more diuretic administration had a lower adjusted odds ratio for death (80). Although even this trial is not definitive, it suggested that prior reported adverse outcomes from diuretic use in AKI likely did reflect confounding by indication. At this point, it seems reasonable to use diuretics as an adjunct in AKI to maintain euvolemia. It is generally best, however, to avoid very high doses, and avoid using diuretics to delay more definitive treatments, such as dialysis.

Summary

Diuretic drugs, agents that target solute transport along the nephron, are used commonly in individuals with normal or reduced kidney function. Each diuretic drug has a unique pharmacokinetic profile, but such differences may not receive sufficient consideration when the drugs are used therapeutically. Recent large, clinical trials now provide an evidence base for diuretic treatment of heart failure. Yet, even when such evidence is available, a deep understanding of diuretic pharmacokinetics and pharmacodynamics enhances the clinical approach to diuresis. As the drugs have substantial ability to ameliorate breathlessness and edema, the goal of optimizing their use should improve patient-focused clinical outcomes. The development of diuretic drugs has been one of

the greatest accomplishments of scientific medicine; the persistence of disorders of ECF volume into the 21st century means that these drugs will continue to play central roles in medical practice for the foreseeable future.

Disclosures

Dr. Ellison has nothing to disclose.

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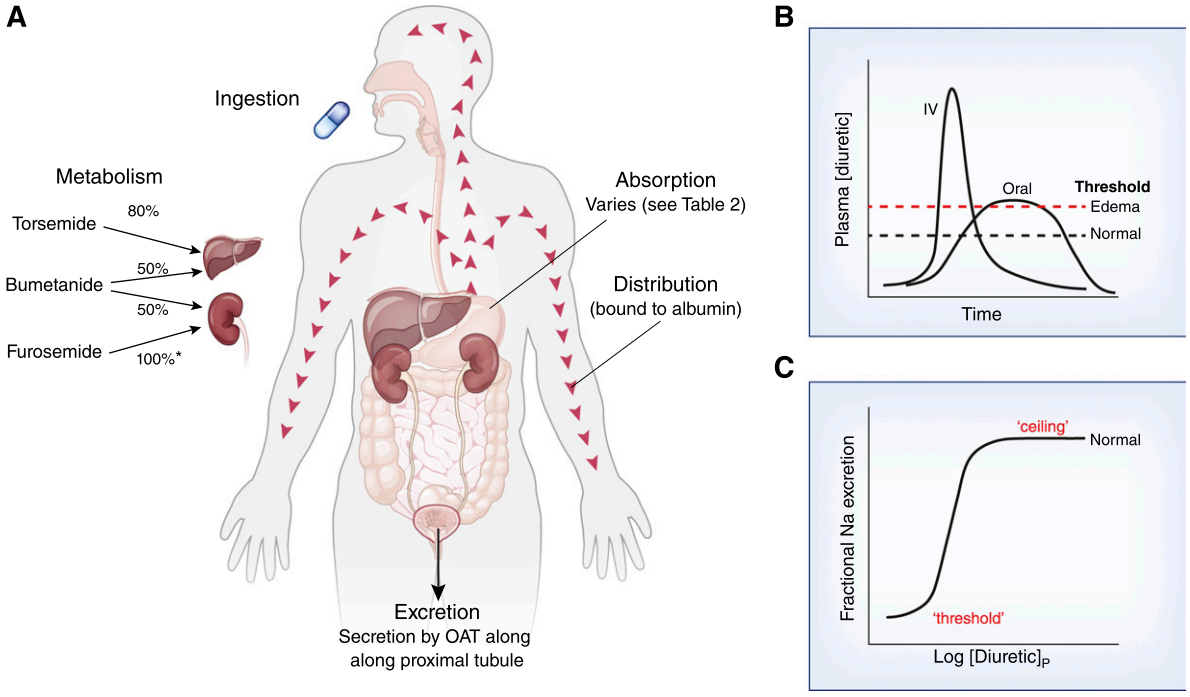
Correction

Ellison DH: Clinical Pharmacology in Diuretic Use. *Clin J Am Soc Nephrol* 14: 1248–1257, 2019; DOI: https://doi.org/10.2215/CJN.09630818.

Because of author error, the following corrections have been issued for this article:

1. The label for "Absorption Varies" in Figure 2A should have referenced Table 2, not Table 1. The corrected Figure 2 is reprinted below.



2. The authors have also reported the following typographical error on page 1251: "antinatriuresis" should have been "natriuresis." The corrected word is in boldface font *in situ* in the paragraph below from the article.

"There are additional reasons that CKD is a loop diuretic–resistant state. Metabolic acidosis, which is frequently observed in uremia, depolarizes the membrane potential of proximal tubule cells (37), which also decreases organic anion secretion, an effect that may explain why diuretic secretion is enhanced by alkalosis (38). In addition to a shift in the dose-response curve, patients with CKD and those taking NSAIDs have a downward shift of

the ceiling natriuresis, when expressed as absolute sodium excretion (rather than fractional). The mechanism for resistance attributable to NSAIDs is complex. Loop diuretic inhibition of NaCl reabsorption at the macula densa stimulates both renin secretion and prostaglandin (PG) production, the latter predominantly via cyclooxygenase-2 (39). When this happens, PG E2 feeds back on tubules, contributing to the resulting natriuresis by inhibiting NaCl transport along the thick ascending limb and collecting duct (40,41). NSAIDs block this PG-mediated **[natriuresis]**. When used chronically, NSAIDs increase the abundance and activity of NKCC2 along the thick ascending limb (42). Additionally, loop diuretics inhibit the second transporter isoform, NKCC1, mentioned above, which is also expressed by vascular smooth muscle cells; loop diuretics contribute to afferent arteriolar vasodilation by blocking this transporter (43), thus helping to maintain GFR despite a lower ECF volume. Again, this compensatory adaptation is largely dependent on PG production and can be blocked by NSAIDs. The clinical consequence of these effects is evident in the association between recent use of NSAIDs and risk for hospitalization in patients with heart failure (34). In fact, the combination of three classes of drugs that affect hemodynamics of the kidney, loop diuretics, angiotensin-converting inhibitors (or receptor blockers), and NSAIDs, is associated with AKI (44).”

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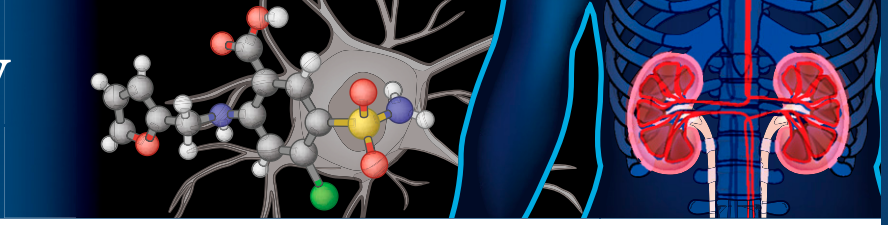

Biosimilars—Emerging Role in Nephrology

Jay B. Wish

Abstract

The Food and Drug Administration (FDA) defines a "biosimilar" agent as a biologic that is highly similar to the reference or originator biologic product notwithstanding minor differences in clinically inactive components with no clinically meaningful differences in terms of the safety, purity, and potency. The advantage of biosimilars is that they are usually about 15%–30% less expensive than the reference product, which results in system-wide cost savings and increased patient access. Because biologic drugs are produced by living organisms, they are by nature heterogeneous and identical copies cannot be made, unlike generic versions of small-molecule drugs. Proposed biosimilars must undergo a rigorous evaluation process to demonstrate a high degree of structural and functional similarity with the reference biologic. Once that is confirmed, a stepwise process of comparison with the reference agent with regard to animal trials, pharmacokinetics/pharmacodynamics, immunogenicity, and human efficacy/safety is conducted. The experience with biosimilars in other highly regulated markets where patent protection for originator biologics is not as robust as in the United States has been favorable in terms of safety, efficacy, and cost savings. An FDA approval pathway was created in 2009 to expedite the approval of biosimilars; as of early 2018 nine agents had been approved through that pathway, none in nephrology. The first United States biosimilar epoetin was approved on May 15, 2018, but does not have an interchangeability designation, meaning that prescribers must specifically write for the biosimilar product for patients to receive it. Given the unfamiliarity of biosimilars within the nephrology community it is recommended that educational programs be developed to address this unmet need and for research to be conducted addressing the perceptual, clinical, and economic effect of biosimilars on our patients.

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Introduction

A "biological product" is defined by the Food and Drug Administration (FDA) as a "virus, therapeutic serum, toxin, antitoxin, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product … applicable to the prevention, treatment of cure of a disease or condition of human beings." (1) Indications for currently available biologic drugs include cell therapy for cancer; clotting factors for hemophilia; cytokine or growth factors for cancer and hepatitis C; enzymes for hereditary deficiencies; mAb for arthritis, lupus, psoriasis, inflammatory bowel disease, multiple sclerosis, and cancer; polyclonal antibodies for immunodeficiency; toxins for cosmetic use; hormones; and vaccines for influenza and other viruses (2). Most recognizable to nephrologists is the biologic recombinant human erythropoietin (rHuEPO). Considerably more expensive to develop and produce, biologics are more structurally complex than small-molecule drugs. By 2020, biologics will constitute an estimated 27% of spending on worldwide pharmacologics (3). The top three drugs (on the basis of cost) administered to out-patients in the United States during the first 9 months of 2014 were infliximab, pegfilgrastim, and erythropoietin (4). Because of the high cost of biologics, fewer people may have access to these agents, limiting their benefit and use.

A "biosimilar" agent is defined by the FDA as a biologic that is highly similar to the reference or originator product, with no clinically meaningful differences in terms of the safety, purity, and potency regardless of minor differences in clinically inactive components (1). It is incorrect to use "biosimilar" to characterize any "copy" or replica of a biologic drug whose target is the same as the reference agent, especially copies developed for markets such as Asia, Africa, and Central and South America that are not highly regulated and for which the agent has no proven comparability to the reference drug. Because many countries in these regions do not have a rigorous process for the testing and approval of so-called "biosimilar" agents, the lesser quality and adverse outcomes reported have made many health care providers and regulators skeptical about the safety and efficacy of "biosimilar" agents in general. The term "biosimilar" is correctly attributed to agents approved in highly regulated markets such as the European Union (EU), the United States, Canada, Japan, Australia, and New Zealand. These products must meet strict criteria of quality and comparability to their respective reference biologics; after approval in highly regulated markets, the record of safety and cost savings is encouraging (5).

Because patent protection for originator pharmaceutics is of shorter duration in the EU than the United States, the EU has a longer experience with the approval process and monitoring the safety of biosimilars that dates to 2005. The first biosimilar

epoetins were approved in the EU in 2008. The EU's experience with biosimilars demonstrated cost savings and expansion of patient access without negative effects on patient outcomes, because consistent and appropriate scientific regulatory standards were applied to biosimilars exactly as they are applied to the reference biologics. In 2010, the European Generic Medicines Association reported savings of 1.4 billion euros per year for European health care systems because of the use of biosimilar agents (6). It is forecast that the use of biosimilar agents will lead to savings of 11.8–33.4 billion euros in France, Germany, Italy, Poland, Romania, Spain, France, and the United Kingdom by 2020 (7). On the basis of the benefits realized in Europe, the United States implemented the Biologics Price Competition and Innovation Act (BPCIA) in 2009 to clarify and expedite the approval process for biosimilar agents. Although not as considerable as the cost saving seen with generic small-molecule drugs (which averages 77% in the first year [2]), the Federal Trade Commission anticipated that the availability of biosimilars would significantly reduce the cost of biologics and increase their accessibility (8). Although supporting data are not robust, biosimilars approved in the United States and EU to date have afforded modest cost savings of 15%–30% over their reference agents (9). With originator products lowering their prices to compete with biosimilars, savings may eventually be larger.

Challenges in Producing Biologic and Biosimilar Agents

Biologic drugs vary in size from simple replacement hormones to large complex molecules with extensive post-translational modifications, such as mAb. Advances such as improving process efficiencies, increasing output to meet expanded commercial demand, and taking advantage of process efficiencies result in minor modifications in the manufacturing, packaging, and distribution process (10). The FDA requires manufacturers to demonstrate that production changes do not adversely affect biologic drugs' identity, strength, quality, purity, or potency. Therefore, comparability testing is performed through appropriate analytic testing, functional assays, and, in some cases, animal and/or clinical studies. Comparability testing proves comparability and allows production changes to occur without a completely new product development program. Establishing biosimilarity of an agent by another manufacturer is a form of comparability assessment and the scientific concept is identical. However, demonstrating that a proposed product is biosimilar to a reference product is more complex than assessing comparability of a product before and after a manufacturing change by the same producer; development of a biosimilar product will likely result in a different manufacturing process, because no direct knowledge of the manufacturing procedures for the reference agent is available to the biosimilar developer. Thus, more data and information are required to establish biosimilarity than to establish comparability of a biologic product after a manufacturing change (10).

Biologic drugs are not homogeneous as are small-molecule drugs. Biologics are produced by cellular systems, which are neither perfect nor consistent by nature and invariably have heterogeneity that results from variability in post-translational processes. This is aggravated by fluctuation from even the highest quality manufacturing, packaging, and distribution processes. Therefore, there can be no perfect copy of a biologic drug, a "bioidentical" drug, because even the originator agent does not contain all perfect, identical molecules. The steps in the manufacturing of biologic (originator and biosimilar) drugs are summarized in Figure 1 (11).

The BPCIA

In the United States, two approval tracks for new drugs are available: the "505" pathway established by the Food and Drug Cosmetic Act (new drug application, used for small-molecule drugs and some older biologics approved through this pathway) and the "351" pathway established by the Public Health Service Act (biologic license application, specifically for biologic drugs). In 2009, the United States enacted the BPCIA, which gives the FDA authority to approve a biosimilar drug for which the reference product is a previously licensed biologic approved through the 351 pathway. The BPCIA's 12-year exclusivity to new biologics means the FDA cannot approve a biosimilar until 12 years after approval of the reference product (12). However, as early as 4 years after the approval of the reference product, the developer of a biosimilar agent may submit a 351 pathway application. Developers of biosimilar products can take advantage of BPCIA's abbreviated pathway, 351(k), to streamline the approval of biosimilars of reference products that were approved through a full 351(a) biologic license application. The 351(k) pathway is on the basis of the comparability principle described above for a manufacturing change for a biologic agent (13). The process begins with structural and functional comparison between the biosimilar and reference products. Additional testing will be determined on the basis of analysis and differences between the agents; more rigorous analysis and fewer differences between the agents will likely trigger less testing. Animal data to determine toxicity, immunogenicity, and pharmacokinetics (PK)/pharmacodynamics may be required to assess safety concerns before human testing of biosimilar products. The congruence of the structural/functional analysis, the knowledge base regarding the reference agent and its safety issues, and any residual concerns from the previous steps will determine the extent of human PK/pharmacodynamics testing needed. Human clinical testing will generally be required but, unless significant lingering concerns persist, there should be minimal requirement to establish safety and efficacy independently for the biosimilar agent. Immunogenicity studies may be required, including assessment of binding antibodies and neutralizing antibodies. The FDA will make its determination regarding approval on the basis of the *totality of the evidence* (italics added by the FDA) (10,14) (Figure 2).

Biosimilar Erythropoietins

Unlike rheumatology, gastroenterology, and oncology, there are relatively few biologics that are routinely used in nephrology. Erythropoietins are the most familiar. The United States patent on eculizumab, which is used to treat atypical hemolytic uremic syndrome and off-label to treat

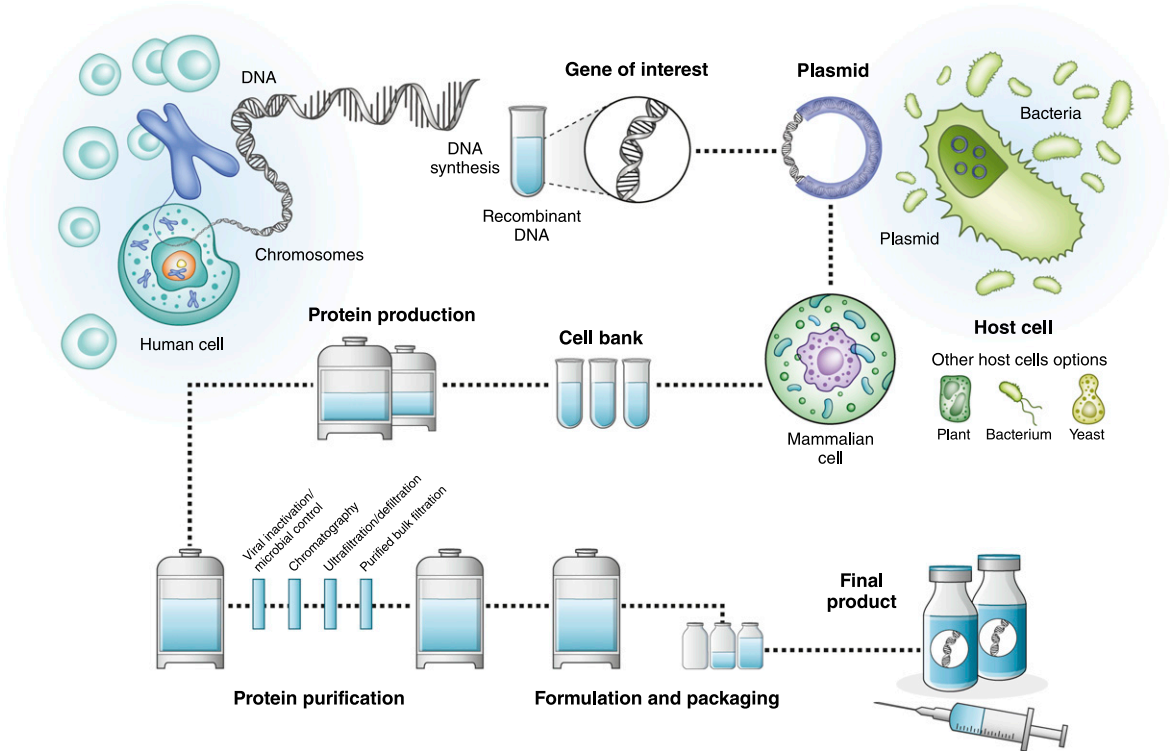

Figure 1. | **The manufacturing of a biologic drug is a highly complex process.** Adapted from Mellstedt, Niederwieser, and Ludwig (11), which is available under the terms of the Creative Commons Attribution License.

membranoproliferative GN, expires in 2021. Amgen and Boston-based Epirus Biopharmaceuticals are developing biosimilar versions of eculizumab and are expected to file for FDA approval in 2020 (15). The United States patent on rituximab, which is used off-label to treat a number of glomerular diseases, expired in 2016. A proposed biosimilar for rituximab sponsored by Sandoz was accepted for review by the FDA in September of 2017. The Sandoz biosimilar rituximab was approved in the EU in June of 2017 (16). Published data regarding biosimilar rituximab are confined to its use in B-cell lymphomas and rheumatoid arthritis with none in glomerular diseases. A biosimilar version of baziliximab, used for prophylaxis of kidney transplant rejection, is under development in China; without a United States development program it is unlikely to be approved by the FDA (17). The patent on belatacept, also used for prophylaxis of kidney transplant rejection, does not expire until 2024 and no biosimilar versions are currently under development. The status of biosimilar development of these agents and the erythropoietins is summarized in Table 1 (15–18).

The United States patent on epoetin alfa, a form of rHuEPO developed by Amgen and introduced in 1989 (19), expired in 2013. Darbepoetin's EU patent expired in 2016 but its United States patent does not expire until 2024. All rHuEPOs have the same amino acid structure, but rHuEPOs made from different cell lines can differ in their carbohydrate structure which may affect their PK and potency. There are two epoetin biosimilars approved in the EU since 2008 for which there is considerable clinical experience: HX575 and SB309. Both of these agents have undergone clinical trials in the United States in anticipation of submission to the FDA for approval through the 351(k) pathway. Sandoz, the sponsor of HX575 in the United States, markets the agent in the EU under the international nonproprietary name epoetin alfa and trade name Binocrit; Hospira/Pfizer, the sponsor of SB309 in the United States, markets the agent in the EU under the international nonproprietary name epoetin zeta and trade name Retacrit. In late 2017, Sandoz abandoned its United States development program for epoetin alfa, leaving epoetin zeta as the only proposed biosimilar epoetin in the United States. Hospira/Pfizer submitted its FDA application for epoetin zeta under the name epoetin hospira. On June 23, 2017, the FDA issued a complete response letter to the epoetin hospira application citing manufacturing concerns in Pfizer's fill-finish facility in Kansas (20). The FDA issued final approval for epoetin hospira on May 15, 2018, under the generic name epoetin alfa-epbx and the brand name Retacrit. The epoetin hospira application to the FDA was supported by four human studies summarized in Table 2 (21).

Because biologics are proteins that can be recognized as "foreign" by the body, immunogenicity is always a concern with these agents, especially with recombinant erythropoietins which may induce anti-drug antibodies that cross-react with native erythropoietin and lead to pure red cell aplasia (PRCA). A cluster of PRCA cases was identified in the EU between 1998 and 2002 after a manufacturing change with an originator epoetin, Eprex, and which occurred only when the drug was administered subcutaneously (SC). The problem was identified and solved, but it

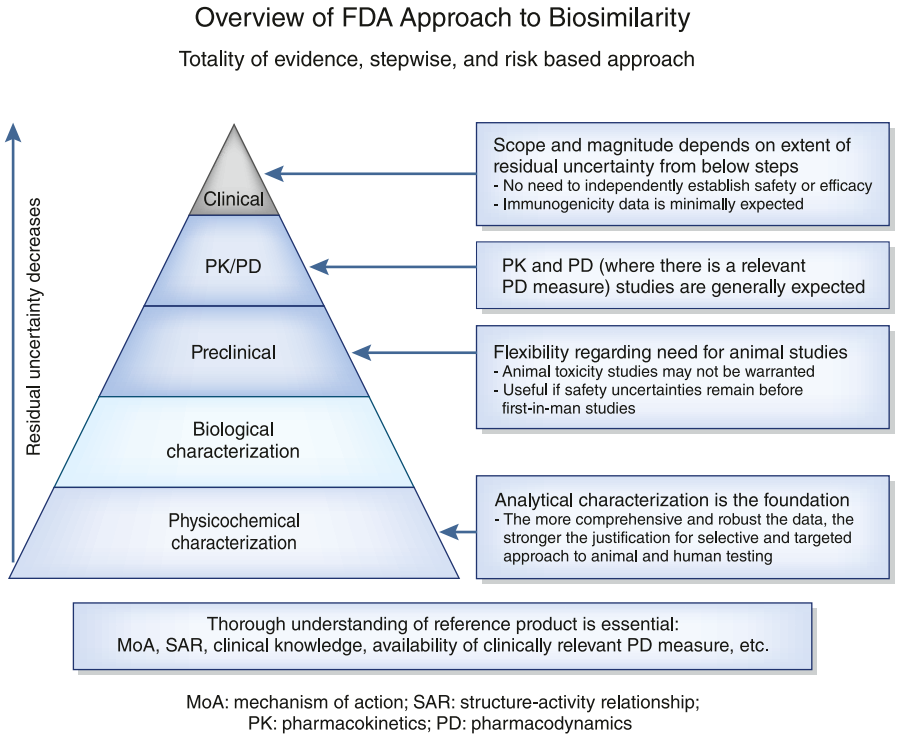

Figure 2. | Approval of a biosimilar product is a stepwise process with greatest emphasis on structural and functional similarity to the reference product. Reprinted from reference (14), with permission.

led European health authorities to contraindicate SC administration of Eprex for patients with CKD from 2002 to 2006 (22). Two cases of PRCA occurred when a biosimilar epoetin (Binocrit) in Europe interacted with the tungsten used to manufacture prefilled syringes (23). The problem was quickly identified and solved, but the EU withheld approval for SC Binocrit administration until 2016. These episodes reinforce the fragility of the manufacturing, packaging, and distribution process for biologic agents with regard to immunogenicity, even within highly regulated markets such as the EU. In the less well regulated market of Thailand, Praditpornsilpa *et al.* (24) noted an alarming increase in the prevalence of PRCA to one in 2068 patients at risk, concomitant with the increased penetration of "biosimilar" epoetins in the market. However, these are not true "biosimilar" products but rather biosimilar-like drugs developed in less regulated markets and the worrisome immunogenicity of the latter should not be confused with the very low immunogenicity of highly regulated products. Patients receiving epoetin hospira in the United States registration trials had comparable low rates (<4%) of anti-drug antibody (non-neutralizing

Table 1. Biologic products used in nephrology

Agent	On-Label Indication	Off-Label Indication	United States Patent Expiration	Biosimilar in Development
Epoetin	Anemia		2013	Pfizer/Hospira; approved by FDA in May 2018
Darbepoetin	Anemia		2024	Already in use in other parts of the world
Eculizumab	Atypical hemolytic uremic syndrome	Membranoproliferative GN	2021	Amgen and Epirus; expected FDA filing in 2020
Rituximab		Glomerular diseases	2016	Sandoz; filed with FDA in 2017
Basiliximab	Kidney transplant rejection		Not available	Sorrento/MabTech; testing in China only
Belatacept	Kidney transplant rejection		2023	None

FDA, Food and Drug Administration.

Table 2. United States epoetin hospira human studies

Study Number	Description	*N*	Predefined End Points	Results	Adverse Events
EPOE-12–02	Single-center, open-label, randomized PK/PD study of epoetin hospira versus Epogen/Procrit after single 100 U/kg SC dose in healthy subjects	81	Epoetin AUC and C_{max}; reticulocyte AUEC and E_{max}	PK and PD similarity with 90% CI for ratios of geographic means within 80%–125% as prespecified by FDA	
EPOE-14–01	Single-center, open-label, parallel group PK/PD study of epoetin hospira versus Epogen/Procrit after 100 U/kg SC tiw for 4 wk in healthy subjects	129	Hb AUC at 28 d; epoetin AUC and C_{max} after final dose	PK and PD similarity with 90% CI for ratios of geographic means within 80%–125% as prespecified by FDA	
EPOE-10–13	Randomized, double-blind, parallel group study of SC epoetin hospira versus Epogen/Procrit in patients receiving HD previously receiving iv Epogen/Procrit	246	Mean weekly epoetin dose and mean weekly Hb during last 4 wk of treatment	No clinically meaningful differences	No significant differences
EPOE-10–01	Randomized, double-blind, parallel group study of iv epoetin hospira versus Epogen/Procrit in patients receiving HD previously receiving iv Epogen/Procrit	612	Mean weekly epoetin dose and mean weekly Hb during last 4 wk of treatment	No clinically meaningful differences	No significant differences

PK, pharmacokinetic; PD, pharmacodynamic; SC, subcutaneous; AUC, area under curve; C_{max}, maximum concentration; AUEC, area under effect curve; E_{max}, maximum effect; 90% CI, 90% confidence interval; FDA, Food and Drug Administration; tiw, three times weekly; Hb, hemoglobin level; HD, hemodialysis; iv, intravenous.

and not affecting drug efficacy) production as those receiving Epogen/Procrit in the control arms. No patient in either arm of any of the United States registration trials for epoetin hospira developed neutralizing antibodies or PRCA (21).

Biosimilar Issues of Concern to Nephrologists

Given the relative lack of knowledge regarding biosimilars and a perceived lack of trust by the nephrology community regarding their safety and efficacy, the National Kidney Foundation (NKF) conducted a symposium, *Introduction of Biosimilar Therapeutics into Nephrology Practice in the United States,* in September of 2015 (25). A number of issues were discussed and are summarized below and in Table 3.

Naming of Biosimilars

It was agreed that each biosimilar agent should have a unique name to distinguish it from other biosimilars and the originator drug, even if the biosimilar has been designated as "interchangeable" with the reference product by the FDA (see below). This is extremely important to minimize inadvertent substitution and for pharmacovigilance, meaning if an adverse reaction should occur it will be easier to trace it back to a specific agent. In 2017 the FDA issued final guidance (26) on the naming of biologics and biosimilars in which a core name is followed by a hyphen and a four-letter suffix in lowercase devoid of meaning. A related biologic or biosimilar product will receive the same core name as the originator. If the core name itself includes a suffix (such as "alfa"), that suffix will be retained before the additional four-letter suffix that identifies the specific product. The FDA assigned the generic name epoetin alfa-epbx to epoetin hospira. As of this writing, a suffix for the originator epoetin alfa has not been assigned.

Interchangeability

To meet the higher standard of interchangeability for a biosimilar agent, Section 351(k) (4) of the Public Health Service Act (27) requires an applicant to "demonstrate that the biologic product can be expected to produce the same clinical results as the reference product in any given patient and, if the biologic product is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between the use of the biologic product and the reference product is not greater than the risk of using the reference product without such alteration or switch." The FDA issued draft guidance in January of 2017 to sponsors of biosimilar drugs for demonstrating interchangeability with a reference biologic (28). As of this writing, no biosimilar has been designated interchangeable by the FDA. The sponsors of epoetin hospira did not request interchangeability designation. An FDA designation of interchangeability is not required for a physician's decision to use a biosimilar or to transition patients from a reference biologic to a biosimilar. Physicians (or other prescribers) may prescribe a biosimilar in the same

Table 3. Key biosimilar issues of concern to nephrologists (25)

Key Biosimilar Issues of Concern
Naming of biosimilars
Minimize inadvertent substitution
Maintain pharmacovigilance
Use of shared core name
Unique four-letter suffix, devoid of meaning, for each product (including interchangeable products)
Interchangeability
No sponsor of a biosimilar product has yet requested an interchangeable designation
A single transition from a reference product to a noninterchangeable biosimilar may be appropriate on the basis of the prescriber's clinical judgment
Substitution of a biosimilar for an originator biologic without the prescriber's consent can occur only for an interchangeable biologic (see below)
Substitution
According to the FDA, interchangeable products may be substituted for the reference product without the intervention of the prescribing health care provider
Many states have enacted legislation establishing standards for substitution of biosimilar product to replace the reference biologic
The NKF recommends that patients also be informed of such substitutions by pharmacists, health insurance plans, hospitals, infusion centers, and dialysis care providers
The NKF recommends that when a biosimilar has an established safety record for 5 yr prescribers no longer be routinely informed of such substitutions
Extrapolation
Has not yet been a major issue since registration trials for the first biosimilar with application to nephrology patients (epoetin) were performed in patients with CKD
Extrapolation of indications applies only to FDA-approved uses of the reference biologic, which may (*e.g.*, eculizumab, basiliximab) or may not (*e.g.*, rituximab) include a nephrology indication
Education for providers and patients
Advantages and disadvantages of biosimilars when compared with the reference product
Known and unknown risks of the biosimilar versus the reference product
Extent of clinical experience with the biosimilar versus the reference product
How cost of the product affects its selection
Research and pharmacovigilance
Initial period of postmarketing surveillance for the safety of newly approved biosimilars in the United States should be in the range of 2–4 yr
Additional long-term research will be needed regarding the safety and efficacy of biosimilar agents in general and products in particular
"Hard" outcomes (*e.g.*, hospitalizations, mortality, rate of CKD progression, transplant survival)
Intermediate outcomes (*e.g.*, cardiovascular events, blood counts, chemistries, inflammatory markers, BP, carcinogenesis, immunogenesis)
Efficacy data (blood transfusions, iron requirements, hemoglobin levels, and drug doses in the case of erythropoietins)
Patient-reported outcomes (quality of life, clarity of information presented, and thoughts and beliefs regarding biosimilars)

FDA, Food and Drug Administration; NKF, National Kidney Foundation.

manner as they would prescribe other medications; the prescriber-directed decision may include prescribing a biosimilar for patients currently stable on the reference biologic (*i.e.*, single transition or switch). A single transition from a reference biologic to a biosimilar may be appropriate on the basis of clinical judgment. The designation of interchangeability provides greater confidence that multiple switches between the reference biologic and biosimilar are safe and also allows for substitution of the biosimilar with the reference agent by the pharmacist within the restrictions described below.

Substitution

The rules governing substitution of a biosimilar for a reference biologic apply only to interchangeable biosimilars (of which there are none as of this writing) and are embodied in the pharmacy regulations of individual states. As of April 2017, 27 states and Puerto Rico enacted laws concerning biosimilars and biosimilar substitution. Most of these laws have features in common: (*1*) the biosimilar must be designated "interchangeable" by the FDA, (*2*) the prescriber can prevent the substitution by stating "dispense as written," (*3*) the prescriber must be notified of any substitution made by the pharmacy, and (*4*) the pharmacy must keep a written record of when a biosimilar is substituted for a reference biologic. The NKF workgroup (25) recommended that patients also be informed of a switch between a reference biologic and a biosimilar, irrespective of whether that switch was performed by the prescriber, pharmacy, health insurance plan, hospital, infusion center, or dialysis provider.

Extrapolation

Extrapolation refers to FDA approval of a biosimilar for an indication for which the biosimilar has not undergone clinical trials but for which the reference product has been approved. Extrapolation to nephrologic disease does not yet apply to any biosimilar agents since the registration trials for epoetin hospira were performed in patients with CKD on hemodialysis. It is conceivable that a future

biosimilar will receive a nephrology indication through extrapolation without having performed registration trials in patients with the nephrologic disease. The FDA evaluates extrapolation on the basis of the mechanism of action in each condition for which licensure is sought, the PK and biodistribution of the product in different patient populations, the immunogenicity of the product in different patient populations, differences in expected toxicities in each condition of use and patient population, and any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought (29). Epoetin hospira performed its United States registration trials in anemic patients undergoing hemodialysis and received FDA approval through extrapolation from Epogen/Procrit for treatment of anemia in all stages of CKD, anemia due to zidovudine in patients with HIV-infection, anemia due to chemotherapy in patients with cancer, and reduction of allogeneic red blood cell transfusions in patients undergoing elective, noncardiac, nonvascular surgery (21).

Education

The NKF workgroup (25) agreed that because the concept of biosimilarity is not familiar to most practitioners and patients, a robust educational effort is warranted to inform choices and provide transparency. There may be considerable skepticism regarding the rationale for abandoning a "tried and true" reference product for a biosimilar agent with a limited track record for safety and efficacy merely to provide cost savings that may not accrue to the patient (as in the case of patients with ESKD where the cost of erythropoietins is part of the bundled payment and any savings accrue to the dialysis provider). Educational topics for providers and patients suggested by the NKF workgroup are summarized in Table 3 (25).

Research and Pharmacovigilance

The NKF workgroup (25) agreed that an initial period of postmarketing surveillance for the safety of newly approved biosimilars in the United States should be in the range of 2–4 years, as adopted in Europe. During this period, it is important that Centers for Medicare and Medicaid Services provide a unique billing code for the biosimilar agent so it can be identified should untoward effects occur within a class of agents. Additional long-term research will be needed to provide support regarding the safety and efficacy of biosimilar agents in general and products in particular (see Table 3) (25).

Conclusions

The first biosimilar agent was approved in the United States through the 351(k) pathway in 2015. The FDA approved the first biosimilar epoetin in May 2018 without an interchangeable designation. The adoption of that agent, epoetin hospira (United States brand name Retacrit and generic name epoetin alfa-epbx), will depend largely on decisions by hospitals, infusion centers, pharmacy services, and dialysis providers to promote the use of the biosimilar by substituting it for an originator erythropoietin on its formulary and/or by requiring prior authorization/justification for the use of an originator agent. In any event, because the biosimilar does not have an interchangeable designation, the prescriber must order the biosimilar for it to be administered to the patient. The comfort level that prescribers and patients have with using an unfamiliar biosimilar must be addressed with educational programs regarding the nature of biosimilars and the attributes of the agent in question. It will be important for nephrologists to learn from our counterparts in other specialties who have been using biosimilars for a while. The cost savings for an epoetin biosimilar in patients receiving dialysis will initially accrue to the dialysis providers, but will eventually accrue to the payers such as Centers for Medicare and Medicaid Services as the bundled payment is inevitably rebased. The cost savings for a biosimilar for an agent such as eculizumab, now one of the most expensive drugs in the world, will accrue more directly to patients and will provide access to patients who could not otherwise afford the originator product or its copay. Despite the intent of the BPCIA to accelerate the approval of lower-cost biosimilar agents, United States patients remain at a significant financial disadvantage to their European counterparts because of the longer patent life for originator products in the United States and the inability of United States patients to obtain lower-cost biosimilar agents with a proven safety record from Europe once the patents on the originator products expire in the United States. A patient-centered approach to biosimilar availability in the United States should consider these barriers. Increasing patient access through lower cost is ultimately the promise of biosimilars.

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