Drug Dosing Adjustments in Patients with Chronic Kidney Disease

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Chronic kidney disease affects renal drug elimination and other pharmacokinetic processes involved in drug disposition (e.g., absorption, drug distribution, nonrenal clearance [metabolism]). Drug dosing errors are common in patients with renal impairment and can cause adverse effects and poor outcomes. Dosages of drugs cleared renally should be adjusted according to creatinine clearance or glomerular filtration rate and should be calculated using online or electronic calculators. Recommended methods for maintenance dosing adjustments are dose reductions, lengthening the dosing interval, or both. Physicians should be familiar with commonly used medications that require dosage adjustments. Resources are available to assist in dosing decisions for patients with chronic kidney disease. (Am Fam Physician 2007;75:1487-96. Copyright © 2007 American Academy of Family Physicians.)

ILLUSTRATION BY SCOTT BODELL

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The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) definition of chronic kidney disease is the presence of kidney damage or a reduction in the glomerular filtration rate (GFR) for three months or longer. The K/DOQI chronic kidney disease staging system *(Table 1)* is based on GFR.[1]

Inappropriate dosing in patients with chronic kidney disease can cause toxicity or ineffective therapy. In particular, older patients are at a higher risk of developing advanced disease and related adverse events caused by age-related decline in renal function and the use of multiple medications to treat comorbid conditions. Chronic kidney disease can affect glomerular blood flow and filtration, tubular secretion and reabsorption, and renal bioactivation and metabolism. Drug absorption, bioavailability, protein binding, distribution volume, and nonrenal clearance (metabolism) also can be altered in these patients. Physicians should pay careful attention when considering drug therapies with active or toxic metabolites that can accumulate and contribute to exaggerated pharmacologic effects or adverse drug reactions in patients with chronic kidney disease. *Table 2* includes resources for more information about dosing adjustments in patients with chronic kidney disease.

Estimating GFR and Creatinine Clearance

Dosages of drugs cleared renally are based on renal function (calculated as GFR or creatinine clearance; *Table 3*). These calculations are valid only when renal function is stable and the serum creatinine level is constant.

The K/DOQI clinical practice guideline advocates using the traditional Cockcroft-Gault equation or the Modification of Diet in Renal Disease (MDRD) study equation (full or abbreviated) for routine estimation of GFR.[1] However, in patients with a GFR lower than 60 mL per minute per 1.73 m^2, the MDRD equation has been shown to be superior to the Cockcroft-Gault equation.[2]

Because the production and excretion of creatinine declines with age, normal serum creatinine values may not represent normal renal function in older patients. The MDRD equation has been shown to be the best method for detecting a GFR lower than 90 mL per minute per 1.73 m^2 in older patients.[3]

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*
In patients with chronic kidney disease, over-the-counter and herbal medicine use should be assessed to ensure that medications are indicated; medications with toxic metabolites should be avoided, the least nephrotoxic agents should be used, and alternative medications should be used if potential drug interactions exist.	C	17, 21, 25, 30, 36, 43
Physicians should be aware of drugs with active metabolites that can exaggerate pharmacologic effects in patients with renal impairment.	C	25
Dosages of drugs cleared renally should be adjusted based on the patient's renal function (calculated as creatinine clearance or glomerular filtration rate); initial dosages should be determined using published guidelines and adjusted based on patient response; serum drug concentrations should be used to monitor effectiveness and toxicity when appropriate.	C	1, 4

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1430 or http://www.aafp.org/afpsort.xml.

Dosing Adjustments

Loading doses usually do not need to be adjusted in patients with chronic kidney disease. Published guidelines suggest methods for maintenance dosing adjustments: dose reduction, lengthening the dosing interval, or both.[4] Dose reduction involves reducing each dose while maintaining the normal dosing interval. This approach maintains more constant drug concentrations, but it is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination. Normal doses are maintained with the extended interval method, but the dosing interval is lengthened to allow time for drug elimination before redosing. Lengthening the dosing interval has been associated with a lower risk of toxicities but a higher risk of subtherapeutic drug concentrations, especially toward the end of the dosing interval.

Dosing recommendations for individual drugs can be found in *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*.[4] The guidelines are divided into three broad GFR categories (less than 10 mL per minute per 1.73 m^2, 10 to 50 mL per minute per 1.73 m^2, and more than 50 mL per minute per 1.73 m^2), encompassing an up to 10-fold range in renal function. The guidelines do not correspond with the K/DOQI staging system; therefore, although they can be used for initial dosages, regimens must be individualized further based on patient response and serum drug concentrations.

Table 1. National Kidney Foundation K/DOQI Staging System for Chronic Kidney Disease

Stage	*Description*	*GFR (mL per minute per 1.73 m^2)*
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with a mild decrease in GFR	60 to 89
3	Moderate decrease in GFR	30 to 59
4	Severe decrease in GFR	15 to 29
5	Kidney failure	< 15 (or dialysis)

NOTE: *Chronic kidney disease is defined as the presence of kidney damage or a reduction in GFR for a period of three months or longer.*

K/DOQI = Kidney Disease Outcomes Quality Initiative; GFR = glomerular filtration rate.

Adapted with permission from National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39(2 suppl 1):S46.

ANTIHYPERTENSIVES

Drug dosing requirements for antihypertensives in patients with chronic kidney disease are listed in *Table 4*.[4,5] Thiazide diuretics are first-line agents for treating uncomplicated hypertension,[6] but they are not recommended if the serum creatinine level is higher than 2.5 mg per dL (220 μmol per L) or if the creatinine clearance is lower than 30 mL per minute.[7,8] Loop diuretics are most commonly used to treat uncomplicated hypertension in patients with chronic kidney disease.[6] Although the addition of aldosterone blockers (e.g., spironolactone [Aldactone], eplerenone [Inspra]) has been shown to reduce mortality in patients with severe heart failure,[9,10] potassium-sparing diuretics and aldosterone blockers should be avoided in patients with severe chronic kidney disease because of the rise in serum potassium that typically accompanies renal dysfunction.[11-13]

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are first-line hypertensive agents for patients with type 1 or 2 diabetes mellitus and proteinuria or early chronic kidney disease.[6] These agents reduce blood pressure and proteinuria, slow the progression of kidney disease, and provide long-term cardiovascular protection.

ACE inhibitors and ARBs inhibit the renin-angiotensin-aldosterone system in patients with chronic kidney disease and in patients with normal baseline serum creatinine levels, causing efferent arteriolar dilation. This can cause an acute decline in GFR of more than 15 percent from baseline with proportional elevations in serum creatinine within the first week of initiating therapy.[14-16] This most commonly occurs in patients with congestive heart failure, in patients using concomitant diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs), and in patients receiving high doses of ACE inhibitors or ARBs. In most patients, ACE inhibitors and ARBs can be continued safely if the rise in serum creatinine is less than 30 percent. Typically, the level will return to baseline in four to six weeks.

A common practice is to discontinue ACE-inhibitor and ARB therapy when the serum creatinine level rises more than 30 percent or if the serum potassium level is 5.6 mEq per L (5.6 mmol per L) or higher.[14-16] Because of long-term renoprotective and cardioprotective effects, no patient should be denied an ACE-inhibitor or ARB trial without careful evaluation. Dosages should be titrated carefully and followed by weekly monitoring of renal function and potassium levels until values return to baseline.

Hydrophilic beta blockers (e.g., atenolol [Tenormin], bisoprolol [Zebeta], nadolol [Corgard], acebutolol [Sectral]) are eliminated renally and dosing adjustments are needed in patients with chronic kidney failure.[7] However, metoprolol tartrate (Lopressor), metoprolol succinate (Toprol XL), propranolol (Inderal), and labetalol (Normodyne) are metabolized by the liver and adjustments are not required. Other antihypertensive agents that do not require dosing adjustments include calcium channel blockers, clonidine (Catapres), and alpha blockers.[17]

HYPOGLYCEMIC AGENTS

Drug dosing requirements for hypoglycemic agents in patients with chronic kidney disease are listed in *Table 5*.[4,18,19] Because metformin (Glucophage) is 90 to 100 percent renally excreted,[18] its use is not recommended when the serum creatinine level is

Table 2. Resources for More Information About Dosing Adjustments in Patients with Chronic Kidney Disease

Drug Prescribing in Renal Failure: Dosing Guidelines for Adults Publisher: American College of Physicians PDA download: http://acp.pdaorder.com/pdaorder/-/605920537541/item?oec-catalog-item-id=1028
FDA Center for Food Safety and Applied Nutrition Web site: http://www.cfsan.fda.gov/
FDA MedWatch Web site: http://www.fda.gov/medwatch/index.html
Medline Plus (herbal medicine) Web site: http://www.nlm.nih.gov/medlineplus/herbalmedicine.html
National Center for Complementary and Alternative Medicine Web site: http://www.nccam.nih.gov/
National Kidney Disease Education Program Web site: http://www.nkdep.nih.gov
National Kidney Foundation Web site: http://www.kidney.org/

PDA = personal digital assistant; FDA = U.S. Food and Drug Administration.

Table 3. Equations for Predicting Creatinine Clearance or GFR in Adults with Kidney Disease

Equation	*Variables*	*Sources*
Cockcroft-Gault	Age, weight, sex, serum creatinine	Nephron Information Center Web site: http://www.nephron.com/cgi-bin/CGSI.cgi
Modification of Diet in Renal Disease	Age, sex, race, serum urea nitrogen, serum albumin, serum creatinine	National Kidney Disease Education Program Web site: http://www.nkdep.nih.gov/professionals/gfr_calculators/index.htm Nephron Information Center Web site: http://www.nephron.com/cgi-bin/MDRDSI.cgi

GFR = glomerular filtration rate; PDA = personal digital assistant.

Table 4. Antihypertensive Agents: Dosing Requirements in Patients with Chronic Kidney Disease

Drug	Usual dosage*	Dosage adjustment (percentage of usual dosage) based on GFR (mL per minute per 1.73 m^2)		
		> 50	10 to 50	< 10
ACE inhibitors†				
Benazepril (Lotensin)	10 mg daily	100%	50 to 75%	25 to 50%
Captopril (Capoten)	25 mg every 8 hours	100%	75%	50%
Enalapril (Vasotec)	5 to 10 mg every 12 hours	100%	75 to 100%	50%
Fosinopril (Monopril)‡	10 mg daily	100%	100%	75 to 100%
Lisinopril (Zestril)	5 to 10 mg daily	100%	50 to 75%	25 to 50%
Quinapril (Accupril)	10 to 20 mg daily	100%	75 to 100%	75%
Ramipril (Altace)[5]	5 to 10 mg daily	100%	50 to 75%	25 to 50%
Beta blockers				
Acebutolol (Sectral)	400 to 600 mg once or twice daily	100%	50%	30 to 50%
Atenolol (Tenormin)	5 to 100 mg daily	100%	50%	25%
Bisoprolol (Zebeta)§	10 mg daily	100%	75%	50%
Nadolol (Corgard)[5]	40 to 80 mg daily	100%	50%	25%
Diuretics				
Amiloride (Midamor)	5 mg daily	100%	50%	Avoid
Bumetanide (Bumex)[5]	No adjustment needed	—	—	—
Furosemide (Lasix)[5]	No adjustment needed	—	—	—
Metolazone (Zaroxolyn)	No adjustment needed	—	—	—
Spironolactone (Aldactone)[5]	50 to 100 mg daily	Every 6 to 12 hours	Every 12 to 24 hours	Avoid
Thiazides‖	25 to 50 mg daily	100%	100%	Avoid
Torsemide (Demadex)[5]	No adjustment needed	—	—	—
Triamterene (Dyrenium)	50 to 100 twice daily	100%	100%	Avoid

GFR = glomerular filtration rate; ACE = angiotensin-converting enzyme.

**—Table provides general dosing information; dosages may be different for specific indications.*
†—May need to use lower initial doses in patients receiving diuretics.
‡—Less likely than other ACE inhibitors to accumulate in patients with renal failure. A fixed-dose combination with hydrochlorothiazide should not be used in patients with a creatinine clearance less than 30 mL per minute (0.5 mL per second).
§—Maximal dosage in patients with renal impairment is 10 mg daily.
‖—Thiazides should not be used in patients with a creatinine clearance less than 30 mL per minute; however, thiazides are effective in these patients when used with loop diuretics.

Information from references 4 and 5.

higher than 1.5 mg per dL (130 μmol per L) in men or higher than 1.4 mg per dL (120 μmol per L) in women, in patients older than 80 years, or in patients with chronic heart failure.[19] The primary concern about the use of metformin in patients with renal insufficiency is that other hypoxemic conditions (e.g., acute myocardial infarction, severe infection, respiratory disease, liver disease) increase the risk of lactic acidosis. Physicians may be apprehensive to maximize the use of metformin in appropriate patients because of these contraindications.

A Cochrane review showed that lactic acidosis did not occur in the more than 20,000 patients with type 2 diabetes studied (patients with standard contraindications to metformin were not included).[20] Rather than avoid the drug completely in patients with chronic kidney disease, it would be reasonable to start with a low dose in these patients and titrate, with close monitoring, based on patient response and tolerability. A more common practice is to temporarily discontinue metformin therapy in patients at a higher risk of lactic acidosis, such as patients who become septic.

Sulfonylureas (e.g., chlorpropamide [Diabinese], glyburide [Micronase]) should be avoided in patients with stages 3 to 5 chronic kidney disease.[18] The half-life of chlorpropamide is significantly increased in these patients, which can cause severe hypoglycemia.[18] Glyburide has an active

Table 5. Hypoglycemic Agents: Dosing Requirements in Patients with Chronic Kidney Disease

Drug	*Usual dosage**	*Special considerations*
Acarbose (Precose)	Maximum: 50 to 100 mg three times daily	Lack of data in patients with a serum creatinine level higher than 2 mg per dL (180 µmol per L); therefore, acarbose should be avoided in these patients[18]
Chlorpropamide (Diabinese)	100 to 500 mg daily	Avoid in patients with a glomerular filtration rate less than 50 mL per minute because of the increased risk of hypoglycemia[19]
Glipizide (Glucotrol)	5 mg daily	Dosage adjustment not necessary in patients with renal impairment
Glyburide (Micronase)	2.5 to 5 mg daily	50 percent of the active metabolite is excreted via the kidney, creating a potential for severe hypoglycemia; not recommended when creatinine clearance is less than 50 mL per minute (0.83 mL per second)[18]
Metformin (Glucophage)	500 mg twice daily	Avoid if serum creatinine level is higher than 1.5 mg per dL (130 µmol per L) in men or higher than 1.4 mg per dL (120 µmol per L) in women, and in patients older than 80 years or with chronic heart failure; fixed-dose combination with metformin should be used carefully in renal impairment; metformin should be temporarily discontinued for 24 to 48 hours before use of iodinated contrast agents, not restarted for 48 hours afterward, and then restarted only when renal function has normalized[19]
Metformin (extended release)	500 mg daily	

*—Table provides general dosing information; dosages may be different for specific indications.

Information from references 4, 18, and 19.

metabolite that is eliminated renally, and accumulation of this metabolite can cause prolonged hypoglycemia in patients with chronic kidney disease.[18] Glipizide, however, does not have an active metabolite and is safe in these patients.[18]

ANTIMICROBIALS

Many antimicrobial agents *(Table 6[4,21])* are eliminated renally and require dosing adjustments in patients with chronic kidney disease; however, several commonly used agents do not require adjustments.[21]

Excessive serum levels of injectable penicillin G or carbenicillin (not available in the United States) may be associated with neuromuscular toxicity, myoclonus, seizures, or coma.[22] Imipenem/cilastatin (Primaxin) can accumulate in patients with chronic kidney disease, causing seizures if doses are not reduced.[23] Patients with advanced disease should receive a different carbapenem, such as meropenem (Merrem).[24] Tetracyclines, with the exception of doxycycline (Vibramycin), have an antianabolic effect that may significantly worsen the uremic state in patients with severe disease. Nitrofurantoin (Furadantin) has a toxic metabolite that can accumulate in patients with chronic kidney disease, causing peripheral neuritis.[25]

Aminoglycosides should be avoided in patients with chronic kidney disease when possible. If used, initial doses should be based on an accurate GFR estimate. Renal function and drug concentrations should be monitored and dosages adjusted accordingly.

ANALGESICS

Patients with stage 5 kidney disease are more likely to experience adverse effects from opioid use. Metabolites of meperidine (Demerol), dextropropoxyphene (propoxyphene [Darvon]), morphine (Duramorph), tramadol (Ultram), and codeine can accumulate in patients with chronic kidney disease, causing central nervous system and respiratory adverse effects.[26-28] These agents are not recommended in patients with stage 4 or 5 disease. A 50 to 75 percent dose reduction for morphine and codeine is recommended in patients with a creatinine clearance less than 50 mL per minute (0.83 mL per second).[28] Extended-release tramadol should be avoided in patients with chronic kidney disease. The dosing interval of tramadol (regular release) may need to be increased to every 12 hours in patients with a creatinine clearance less than 30 mL per minute (0.5 mL per second).[29] Acetaminophen can be used safely in patients with renal impairment.

NSAIDS

Adverse renal effects of NSAIDs include acute renal failure; nephrotic syndrome with interstitial nephritis; and chronic renal

Table 6. Antimicrobial Agents: Dosing Requirements in Patients with Chronic Kidney Disease

Drug	*Usual dosage*	*Dosage adjustment (percentage of usual dosage) based on GFR (mL per minute per 1.73 m²)*		
		> 50	*10 to 50*	*< 10*
Antifungals				
Fluconazole (Diflucan)	200 to 400 mg every 24 hours	100%	50%	50%
Itraconazole (Sporanox)	100 to 200 mg every 12 hours	100%	100%	50% (IV form is contraindicated)
Ketoconazole (Nizoral)	No adjustment needed	—	—	—
Miconazole (Monistat)	No adjustment needed	—	—	—
Antivirals				
Acyclovir IV (Zovirax)*	5 to 10 mg per kg every 8 hours	100%	100% every 12 to 24 hours	50% every 12 to 24 hours
Acyclovir (oral)	200 to 800 mg every 4 to 12 hours	100%	100%	200 mg every 12 hours
Valacyclovir (Valtrex)	500 mg every 12 hours to 1,000 mg every 8 hours, depending on indication	100%	100% every 12 to 24 hours	500 mg every 24 hours
Carbapenems				
Ertapenem (Invanz)	1 g every 24 hours	100%	100%	50%
Imipenem	0.25 to 1 g every 6 hours	100%	50%	25%
Meropenem (Merrem)	1 to 2 g every 8 hours	100%	50% every 12 hours	50% every 24 hours (GFR < 20)
Cephalosporins				
Cefaclor (Ceclor)	250 to 500 mg every 8 hours	100%	50 to 100%	50%
Cefadroxil (Duricef)	0.5 to 1 g every 12 hours	100%	Every 12 to 24 hours	Every 36 hours
Cefamandole (Mandol)	0.5 to 1 g every 4 to 8 hours	Every 6 hours	Every 6 to 8 hours	Every 8 to 12 hours
Cefazolin (Ancef)	0.25 to 2 g every 6 hours	Every 8 hours	Every 12 hours	50% every 24 to 48 hours
Cefepime (Maxipime)	0.25 to 2 g every 8 to 12 hours	100%	50 to 100% every 24 hours	25 to 50% every 24 hours
Cefixime (Suprax)	200 mg every 12 hours	100%	75%	50%
Cefoperazone (Cefobid)	No adjustment needed	—	—	—
Cefotaxime (Claforan)	1 to 2 g every 6 to 12 hours	Every 6 hours	Every 6 to 12 hours	Every 24 hours or 50%
Cefotetan (Cefotan)	1 to 2 g every 12 hours	100%	Every 24 hours	Every 48 hours
Cefoxitin (Mefoxin)	1 to 2 g every 6 to 8 hours	Every 6 to 8 hours	Every 8 to 12 hours	Every 24 to 48 hours
Cefpodoxime (Vantin)	100 to 400 mg every 12 hours	Every 12 hours	Every 24 hours	Every 24 hours
Cefprozil (Cefzil)	250 to 500 mg every 12 hours	100%	50% every 12 hours	50% every 12 hours
Ceftazidime (Fortaz)	1 to 2 g every 8 hours	Every 8 to 12 hours	Every 12 to 24 hours	Every 24 to 48 hours
Ceftibuten (Cedax)	400 mg every 24 hours	100%	25 to 50%	25 to 50%
Ceftizoxime (Cefizox)	1 to 2 g every 8 to 12 hours	Every 8 to 12 hours	Every 12 to 24 hours	Every 24 hours
Ceftriaxone (Rocephin)	No adjustment needed	—	—	—
Cefuroxime axetil (Ceftin)	No adjustment needed	—	—	—
Cefuroxime sodium (Zinacef)	0.75 to 1.5 g every 8 hours	Every 8 hours	Every 8 to 12 hours	Every 12 hours
Cephalexin (Keflex)	250 to 500 mg every 6 to 8 hours	Every 8 hours	Every 8 to 12 hours	Every 12 to 24 hours
Cephradine (Velosef)	0.25 to 1 g every 6 to 12 hours	100%	50%	25%
Macrolides				
Azithromycin (Zithromax)	No adjustment needed	—	—	—
Clarithromycin (Biaxin)	250 to 500 mg every 12 hours (Biaxin); 1 g daily (Biaxin XL)	100%	50 to 100%	50%
Dirithromycin	No adjustment needed	—	—	—
Erythromycin	No adjustment needed	—	—	—
Penicillins				
Amoxicillin	250 to 500 mg every 8 hours	Every 8 hours	Every 8 to 12 hours	Every 24 hours
Ampicillin	0.25 to 2 g every 6 hours	Every 6 hours	Every 6 to 12 hours	Every 12 to 24 hours

continued

Table 6. Antimicrobial Agents: Dosing Requirements in Patients with Chronic Kidney Disease *(continued)*

Drug	*Usual dosage*	*Dosage adjustment (percentage of usual dosage) based on GFR (mL per minute per 1.73 m²)*		
		> 50	*10 to 50*	*< 10*
Penicillins (continued)				
Ampicillin/sulbactam (Unasyn)	1 to 2 g ampicillin and 0.5 to 1 g sulbactam every 6 to 8 hours	100% (GFR ≥ 30)	Every 12 hours (GFR 15 to 29)	Every 24 hours (GFR 5 to 14)
Carbenicillin (Geocillin), 382-mg tablet	1 or 2 tablets every 6 hours	Every 6 to 12 hours	Every 12 to 24 hours	Every 24 to 48 hours
Carbenicillin IV (not available in the United States)	200 to 500 mg per kg per day, continuous infusion or in divided doses	Every 8 to 12 hours	Every 12 to 24 hours	Every 24 to 48 hours
Dicloxacillin (Dynapen)	No adjustment needed	—	—	—
Nafcillin	No adjustment needed	—	—	—
Penicillin G	0.5 to 4 million U every 4 to 6 hours	100%	75%	20 to 50%
Penicillin VK	No adjustment needed	—	—	—
Piperacillin	3 to 4 g every 6 hours	Every 6 hours	Every 6 to 12 hours	Every 12 hours
Piperacillin/tazobactam (Zosyn)	3.375 to 4.5 g every 6 to 8 hours	100%	2.25 g every 6 hours; every 8 hours (GFR < 20)	2.25 g every 8 hours
Ticarcillin	3 g every 4 hours	1 to 2 g every 4 hours	1 to 2 g every 8 hours	1 to 2 g every 12 hours
Ticarcillin/clavulanate (Timentin)	3.1 g every 4 hours	100%	Every 8 to 12 hours	2 g every 12 hours
Quinolones				
Ciprofloxacin (Cipro)	400 mg IV or 500 to 750 mg orally every 12 hours	100%	50 to 75%	50%
Gatifloxacin (Tequin)	400 mg every 24 hours	100%	400 mg initially, then 200 mg daily	400 mg initially, then 200 mg daily
Gemifloxacin (Factive)	320 mg every 24 hours	100%	50 to 100%	50%
Levofloxacin (Levaquin)	250 to 750 mg every 24 hours	100%	500 to 750 mg initial dose, then 250 to 750 mg every 24 to 48 hours	500 mg initial dose, then 250 to 500 mg every 48 hours
Moxifloxacin (Avelox)	No adjustment needed	—	—	—
Norfloxacin (Noroxin)	400 mg every 12 hours	Every 12 hours	Every 12 to 24 hours	Avoid
Ofloxacin (Floxin)	200 to 400 mg every 12 hours	100%	200 to 400 mg every 24 hours	200 mg every 24 hours
Trovafloxacin (not available in the United States)	No adjustment needed	—	—	—
Sulfas				
Sulfamethoxazole (Gantanol)	1 g every 8 to 12 hours	Every 12 hours	Every 18 hours	Every 24 hours
Sulfisoxazole (Gantrisin)	1 to 2 g every 6 hours	Every 6 hours	Every 8 to 12 hours	Every 12 to 24 hours
Trimethoprim (Proloprim)	100 mg every 12 hours	Every 12 hours	Every 12 hours (GFR > 30); every 18 hours (GFR 10 to 30)	Every 24 hours
Tetracyclines				
Doxycycline (Vibramycin)	No adjustment needed	—	—	—
Tetracycline	250 to 500 mg two to four times daily	Every 8 to 12 hours	Every 12 to 24 hours	Every 24 hours
Other				
Chloramphenicol (Chloromycetin)	No adjustment needed	—	—	—
Clindamycin (Cleocin)	No adjustment needed	—	—	—
Dalfopristin/quinupristin (Synercid)	No adjustment needed	—	—	—
Linezolid (Zyvox)	No adjustment needed	—	—	—
Nitrofurantoin (Furadantin)	500 to 1,000 mg every 6 hours	100%	Avoid	Avoid
Telithromycin (Ketek)	No adjustment needed	—	—	—

GFR = glomerular filtration rate; IV = intravenous.

**—To avoid nephrotoxicity it is recommended that the patient have a daily urine output of 1 mL for every 1.3 mg of acyclovir administered.*

Adapted with permission from Livornese LL Jr, Slavin D, Gilbert B, Robbins P, Santoro J. Use of antibacterial agents in renal failure. Infect Dis Clin North Am 2004;18:556-67, with additional information from reference 4.

Table 7. Statins: Dosing Requirements in Patients with Chronic Kidney Disease

Drug	*Usual dosage*[38]	*Dosage adjustments based on degree of renal function*
Atorvastatin (Lipitor)	10 mg daily Maximal dosage: 80 mg daily	No adjustment needed
Fluvastatin (Lescol)	20 to 80 mg daily 80 mg daily (sustained release)	50% dose reduction in patients with a GFR less than 30 mL per minute per 1.73 m^2
Lovastatin (Mevacor)	20 to 40 mg daily Maximal dosage: 80 mg daily (immediate release) or 60 mg daily (extended release)	Use with caution in patients with a GFR less than 30 mL per minute per 1.73 m^2
Pravastatin (Pravachol)	10 to 20 mg daily Maximal dosage: 40 mg daily	Starting dosage should not exceed 10 mg daily in patients with a GFR less than 30 mL per minute per 1.73 m^2
Rosuvastatin (Crestor)	5 to 40 mg daily	Recommended starting dosage is 5 mg daily in patients with a GFR less than 30 mL per minute per 1.73 m^2 not to exceed 10 mg daily
Simvastatin (Zocor)	10 to 20 mg daily Maximal dosage: 80 mg daily	Recommended starting dosage is 5 mg daily in persons with a GFR less than 10 mL per minute per 1.73 m^2

GFR = glomerular filtration rate.

**—Table provides general dosing information; dosages may be different for specific indications.*

Information from references 37 and 38.

Table 8. Other Common Agents: Dosing Requirements in Patients with Chronic Kidney Disease

		Dosage adjustments based on (percentage of usual dosage) GFR (mL per minute per 1.73 m^2)		
Drug	*Usual dosage**	*> 50*	*10 to 50*	*< 10*
Allopurinol (Zyloprim)†	300 mg daily	75%	50%	25%
Esomeprazole (Nexium)	No adjustment needed	—	—	—
Famotidine (Pepcid)	20 to 40 mg at bedtime	50%	25%	10%
Gabapentin (Neurontin)[39]	300 to 600 mg three times daily	900 to 3,600 mg three times daily (GFR ≥ 60)	400 to 1,400 mg twice daily (GFR > 30 to 59) 200 to 700 mg daily (GFR > 15 to 29)	100 to 300 mg daily (GFR ≤ 15)
Lansoprazole (Prevacid)	No adjustment needed	—	—	—
Metoclopramide (Reglan)	10 to 15 mg three times daily	100%	75%	50%
Omeprazole (Prilosec)	No adjustment needed	—	—	—
Ranitidine (Zantac)	150 to 300 mg at bedtime	75%	50%	25%

GFR = glomerular filtration rate.

**—Table provides general dosing information; dosages may be different for specific indications.*
†—Elimination half-life of active metabolite oxypurinol increases from 24 hours to 125 hours in patients with renal failure. Accumulation of oxypurinol can lead to a toxic immune mediated reaction.

Information from references 4 and 39.

failure with or without glomerulopathy, interstitial nephritis, and papillary necrosis.[30] The risk of acute renal failure is three times higher in NSAID users than in non-NSAID users.[31] Other adverse effects of NSAIDs include decreased potassium excretion, which can cause hyperkalemia, and decreased sodium excretion, which can cause peripheral edema, elevated blood pressure, and decompensation of heart failure. NSAIDs can blunt antihypertensive treatment, especially if beta blockers, ACE inhibitors, or ARBs are used.[32,33] Although selective cyclooxygenase-2 (COX-2) inhibitors may cause slightly fewer

adverse gastrointestinal effects, adverse renal effects are similar to traditional NSAIDs.[34,35]

Short-term use of NSAIDs is generally safe in patients who are well hydrated; who have good renal function; and who do not have heart failure, diabetes, or hypertension.[36] Long-term use and high daily dosages of COX-2 inhibitors and other NSAIDs should be avoided if possible. Patients at high risk of NSAID-induced kidney disease should receive serum creatinine measurements every two to four weeks for several weeks after initiation of therapy because renal insufficiency may occur early in the course of therapy.

OTHER MEDICATIONS

Drug dosing requirements for statins and for other commonly prescribed medications that require dosing adjustments in patients with chronic kidney disease are listed in *Table 7*[37,38] and *Table 8*,[4,39] respectively.

Although herbal therapies are commonly used,[40] some may pose a risk in patients with chronic kidney disease. St. John's wort and ginkgo accelerate the metabolism of many medications, causing diminished pharmacologic effects. Ginkgo also can increase the risk of bleeding in patients taking aspirin, ibuprofen, or warfarin (Coumadin). Some herbal products (e.g., alfalfa, dandelion, noni juice) contain undisclosed amounts of potassium, which can cause hyperkalemia. Some may contain heavy metals that are toxic to the kidneys, or ephedra-like vasoconstrictive compounds that can cause hypertension.[41-43] Chinese herbal medicines containing aristolochic acid (commonly used in weight-loss regimens) are nephrotoxic and can cause stage 5 kidney disease.[3]

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REFERENCES

1. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002;39 (2 suppl 1):S1-266.
2. Poggio ED, Wang X, Greene T, Van Lente F, Hall PM. Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 2005;16:459-66.
3. Burkhardt H, Hahn T, Gretz N, Gladisch R. Bedside estimation of the glomerular filtration rate in hospitalized elderly patients. Nephron Clin Pract 2005;101:c1-8.
4. Aronoff GR. Drug Prescribing in Renal Failure: Dosing Guidelines for Adults. 4th ed. Philadelphia, Pa.: American College of Physicians, 1999.
5. Saseen JJ, Carter BL. Hypertension. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy. 6th ed. New York, N.Y.: McGraw-Hill, 2005:185-215.
6. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL Jr, et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report [Published correction appears in JAMA 2003;290:197]. JAMA 2003;289:2560-72.
7. Carter BL. Dosing of antihypertensive medications in patients with renal insufficiency. J Clin Pharmacol 1995;35:81-6.
8. Brater DC. Diuretic therapy. N Engl J Med 1998;339: 387-95.
9. Pitt B, Zannad F, Remme WJ, Cody R, Castaigne A, Perez A, et al., for the Randomized Aldactone Evaluation Study Investigators. The effect of spironolactone on morbidity and mortality in patients with severe heart failure. N Engl J Med 1999;341:709-17.
10. Pitt B, Remme W, Zannad F, Neaton J, Martinez F, Roniker B, et al., for the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study Investigators. Eplerenone, a selective aldosterone blocker, in patients with left ventricular dysfunction after myocardial infarction [Published correction appears in N Engl J Med 2003;348:2271]. N Engl J Med 2003;348:1309-21.
11. Juurlink DN, Mamdani MM, Lee DS, Kopp A, Austin PC, Laupacis A, et al. Rates of hyperkalemia after publication of the Randomized Aldactone Evaluation Study. N Engl J Med 2004;351:543-51.

12. Palmer BF. Managing hyperkalemia caused by inhibitors of the renin-angiotensin-aldosterone system. N Engl J Med 2004;351:585-92.
13. Hu Y, Carpenter JP, Cheung AT. Life-threatening hyperkalemia: a complication of spironolactone for heart failure in a patient with renal insufficiency. Anesth Analg 2002;95:39-41.
14. Bakris GL, Weir MR. Angiotensin-converting enzyme inhibitor–associated elevations in serum creatinine: is this a cause for concern? Arch Intern Med 2000;160:685-93.
15. Ahmed A. Use of angiotensin-converting enzyme inhibitors in patients with heart failure and renal insufficiency: how concerned should we be by the rise in serum creatinine? J Am Geriatr Soc 2002;50:1297-300.
16. Palmer BF. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers: what to do if the serum creatinine and/or serum potassium concentration rises. Nephrol Dial Transplant 2003;18:1973-5.
17. Kappel J, Calissi P. Nephrology: 3. Safe drug prescribing for patients with renal insufficiency. CMAJ 2002;166:473-7.
18. Snyder RW, Berns JS. Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. Semin Dial 2004;17:365-70.
19. Metformin (Glucophage) [Package insert]. Princeton, N.Y.: Bristol-Myers Squibb, June 2006.
20. Salpeter S, Greyber E, Pasternak G, Salpeter E. Risk of fatal and nonfatal lactic acidosis with metformin use in type 2 diabetes mellitus. Cochrane Database Syst Rev 2006(1):CD002967.
21. Livornese LL Jr, Slavin D, Gilbert B, Robbins P, Santoro J. Use of antibacterial agents in renal failure. Infect Dis Clin North Am 2004;18:551-79.
22. Marks MI, Hirshfeld S. Neurotoxicity of penicillin. N Engl J Med 1968;279:1002-3.
23. Gibson TP, Demetriades JL, Bland JA. Imipenem/cilastatin: pharmacokinetic profile in renal insufficiency. Am J Med 1985;78:54-61.
24. Chimata M, Nagase M, Suzuki Y, Shimomura M, Kakuta S. Pharmacokinetics of meropenem in patients with various degrees of renal function, including patients with end-stage renal disease. Antimicrob Agents Chemother 1993;37:229-33.
25. Drayer DE. Pharmacologically active drug metabolites: therapeutic and toxic activities, plasma and urine data in man, accumulation in renal failure. Clin Pharmacokinet 1976;1:426-43.
26. Davies G, Kingswood C, Street M. Pharmacokinetics of opioids in renal dysfunction. Clin Pharmacokinet 1996;31:410-22.
27. Szeto HH, Inturrisi CE, Houde R, Saal S, Cheigh J, Reidenberg MM. Accumulation of normeperidine, an active metabolite of meperidine, in patients with renal failure of cancer. Ann Intern Med 1977;86:738-41.
28. Stock SL, Catalano G, Catalano MC. Meperidine associated mental status changes in a patient with chronic renal failure. J Fla Med Assoc 1996;83:315-9.
29. Murphy EJ. Acute pain management pharmacology for the patient with concurrent renal or hepatic disease. Anaesth Intensive Care 2005;33:311-22.
30. Bennett WM, Henrich WL, Stoff JS. The renal effects of nonsteroidal anti-inflammatory drugs: summary and recommendations. Am J Kidney Dis 1996;28 (1 suppl 1):S56-62.
31. Huerta C, Castellsague J, Varas-Lorenzo C, Garcia Rodriguez LA. Nonsteroidal anti-inflammatory drugs and risk of ARF in the general population. Am J Kidney Dis 2005;45:531-9.
32. Johnson AG, Nguyen TV, Day RO. Do nonsteroidal anti-inflammatory drugs affect blood pressure? A meta-analysis. Ann Intern Med 1994;121:289-300.
33. Fogari R, Zoppi A, Carretta R, Veglio F, Salvetti A, for the Italian Collaborative Study Group. Effect of indomethacin on the antihypertensive efficacy of valsartan and lisinopril: a multicentre study. J Hypertens 2002;20:1007-14.
34. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al., for the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000;343:1520-8.
35. Swan SK, Rudy DW, Lasseter KC, Ryan CF, Beuchel KL, Lambrecht LJ, et al. Effect of cyclooxygenase-2 inhibition on renal function in elderly persons receiving a low-salt diet. A randomized, controlled trial. Ann Intern Med 2000;133:1-9.
36. Gambaro G, Perazella MA. Adverse renal effects of anti-inflammatory agents: evaluation of selective and nonselective cyclooxygenase inhibitors. J Intern Med 2003;253:643-52.
37. Weiner DE, Sarnak MJ. Managing dyslipidemia in chronic kidney disease. J Gen Intern Med 2004;19:1045-52.
38. Talbert RL. Hyperlipidemima. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, eds. Pharmacotherapy. 6th ed. New York, N.Y.: McGraw-Hill, 2005:429-52.
39. Neurontin (Gabapentin) [Package insert]. New York, N.Y.: Parke-Davis. December 2005.
40. Bent S, Ko R. Commonly used herbal medicines in the United States: a review. Am J Med 2004;116:478-85.
41. Mueller BA, Scott MK, Sowinski KM, Prag KA. Noni juice *(Morinda citrifolia):* hidden potential for hyperkalemia? Am J Kidney Dis 2000;35:310-2.
42. Saper RB, Kales SN, Paquin J, Burns MJ, Eisenberg DM, Davis RB, et al. Heavy metal content of ayurvedic herbal medicine products. JAMA 2004;292:2868-73.
43. Isnard Bagnis C, Deray G, Baumelou A, Le Quintrec M, Vanherweghem JL. Herbs and the kidney. Am J Kidney Dis 2004;44:1-11.