Drug Therapy Individualization for Patients with Chronic Kidney Disease

Therapy in Patients with Chronic Kidney Disease (CKD)

- **Individualization of a drug dosage regimen for a patient with reduced kidney function is based on:**

1. **The pharmacodynamics/pharmacokinetics of the drug.**
2. **Residual renal function.**
3. **The overall clinical condition of the patient.**

Therapy in Patients with Chronic Kidney Disease (CKD)

- **In addition to the decrease in renal clearance, non-renal clearance (gastrointestinal and hepatic drug metabolism) of several drugs is also reduced.**

Therapy in Patients with Chronic Kidney Disease

Definition of chronic kidney disease (CKD):

- It is the presence of abnormalities of kidney function or structure.
- In its earliest stages it is characterized by either an estimated glomerular filtration rate (eGFR) < 89 mL/min/1.73 m^2; or the persistence of one or more markers of kidney damage (albuminuria) for more than 3 months in those with eGFR ≥ 90 mL/min/1.73 m^2.

GFR Category	GFR (mL/min/1.73 m^2)	Renal dysfunction
1	>90	Normal function
2	60–89	Mild
3a	45–59	Mild- to -moderate
3b	30–44	Moderate- to - severe
4	15–29	Severe
5	<15	Renal failure

Therapy in Patients with Chronic Kidney Disease

- Medications which are predominantly eliminated unchanged by the kidney may accumulate in CKD patients, which can increase the risk of adverse effects.
- If 30% or more of a drug is eliminated unchanged in the urine, it may require dosage adjustment in CKD patients, especially those with stage 3 - 5 disease.

Therapy in Patients with Chronic Kidney Disease

- Increased or decreased protein binding, altered cytochrome P450 enzyme activity and altered transcellular transport systems that are associated with CKD may affect serum and tissue drug concentrations and necessitate drug dosing adjustments.

Therapy in Patients with Chronic Kidney Disease

- The dosage of many drugs must be altered to prevent toxicity, without compromising the achievement of the desired therapeutic outcome.
- Dangerous dosing errors in CKD patients still occur.

Pharmacokinetic Changes In CKD

Drug Absorption:

- **The absorption and bioavailability of some drugs is highly variable in CKD patients.**
- **The mechanisms responsible are multifactorial and include; drug interactions, delayed gastric emptying, and reduced gastric acidity.**
- **Decreased gastrointestinal (GI) motility secondary to gastroparesis in patients with diabetes may delay the t_{max} (time to peak)and may also reduce the (peak concentration) C_{max}.**

Pharmacokinetic Changes In CKD

- If a drug undergoes GI metabolism, the slower transit time allows for more GI metabolism and thus lower C_{max} of the parent drug.
- Urea retention in CKD patients results in a high influx of urea into the gut, which is converted to ammonia, leading to an increase in gastric pH.
- The increase in gastric pH may alter the dissolution or ionization properties of weakly basic drugs leading to changes in absorption.

Pharmacokinetic Changes In CKD

- **A reduction in gastric acidity, associated with the concomitant administration of antacids, H_2-receptor antagonists, proton pump inhibitors, and phosphate binders reduce the bioavailability of several antibiotics and digoxin.**
- **Antacids and vitamin supplements may decrease the bioavailability of some drugs as a result of the formation of insoluble salts or metal ion chelates.**

Pharmacokinetic Changes In CKD

- **Edema of the GI tract, secondary to cirrhosis or congestive heart failure in CKD patients, can decrease the absorption of some drugs (reduce oral absorption of furosemide from 10 – 50%).**
- **The bioavailablity of only a few drugs (dextropropoxyphene, dihydrocodeine, felodipine, sertraline, and cyclosporine) increases in CKD patients.**
- **This is due to reduction in first-pass metabolism.**

Pharmacokinetic Changes In CKD

- **Drug interactions may independently alter bioavailability.**
- **Bioflavonoids in grapefruit juice inhibit CYP3A4 enzyme and noncompetitively inhibit the metabolism of drugs metabolized by this enzyme; this interaction can increase the bioavailability of cyclosporine by as much as 20%.**

Pharmacokinetic Changes In CKD

Distribution:

- The V_D of many drugs may be increased in categories 3-5 CKD patients leading to a reduction in serum drug concentration.
- The increase in V_D may be due to: fluid overload secondary to excessive fluid administration or intake, decreased protein binding, or increased tissue binding.

Pharmacokinetic Changes In CKD

- **Decreased tissue binding of drugs in CKD patients may result in a reduction in V_D (digoxin and pindolol).**
- **Variability in fluid status is common in patients with severe CKD (category 4 & 5), especially those that are critically ill.**

Changes of Volume of Distribution of Selected Drugs in Patients with ESRD

Increased V_D	Decreased V_D
Aminoglycosides, Cephalosporins, Dicloxacillin, Erythromycin, Furosemide, Isoniazide, Naproxen, Phenytoin, Trimethoprim, Vancomycin…	B-blockers, Ciprofloxacin, Digoxin, Ethambutol, Methicillin…

Pharmacokinetic Changes In CKD

- **Many critically ill patients receive large volumes of IV fluids, and can subsequently develop edema, pleural effusions, or ascites.**
- **These, in addition to reduced water excretion in CKD, may lead to an increase the V_D of water-soluble drugs and decrease their serum concentration (aminoglycosides and cephalosporins V_D may be increased by up to 150%).**

Pharmacokinetic Changes In CKD

Effect of Altered Plasma Protein Binding:

- Only unbound or “free” drug is able to cross cellular membranes and distribute outside the vascular space.
- Many drugs have altered protein binding in CKD patients.
- A result of a decrease in protein binding is an increase in the apparent V_D.

Pharmacokinetic Changes In CKD

- **Protein binding of many acidic drugs is reduced (penicillins, cephalosporins, aminoglycosides, furosemide, and phenytoin) secondary to:**

1. **Hypoalbuminemia.**
2. **Qualitative changes in the conformation of the protein binding site.**
3. **Competition for binding sites by other drugs, metabolites, and endogenous substances.**

Pharmacokinetic Changes In CKD

- **Protein binding of phenytoin (90% protein-bound, primarily to albumin) is significantly reduced secondary to decreased plasma phenytoin binding affinity for albumin, as well as low serum albumin, leading to an increase in the unbound concentration.**
- **These changes alter the relationship between total phenytoin concentration and desired or toxic effects.**

Pharmacokinetic Changes In CKD

- The increase in unbound fraction, from 10% in normal renal function to 20% or more in category 5 CKD, results in increased hepatic clearance and decreased total concentrations.
- Thus, the therapeutic range based on total phenytoin concentration is shifted downward from 10 to 20 mg/L to values as low as 4 to 8 mg/L.
- However, the unbound concentration range remains the same for all patients (normal or CKD).

Pharmacokinetic Changes In CKD

- **One can approximate the total phenytoin concentration that would be observed in category 5 CKD patients if they had normal plasma protein binding ($C_{\text{normal binding}}$).**
- **For albumin expressed in g/L the equation is**

$$C_{\text{total normal binding}} = C_{\text{total reported}} / [(0.9)(0.48)(\text{albumin}/44)] + 0.1$$

Pharmacokinetic Changes In CKD

- The principal binding protein for several basic drugs is α_1-acid glycoprotein, an acute-phase reactant protein, whose plasma concentrations are increased in CKD patients.
- As a result, the unbound fraction of some basic drugs (disopyramide) may be significantly decreased in CKD patients.

Pharmacokinetic Changes In CKD

Effect of Altered Tissue Binding:

- **Few drugs (pindolol, ethambutol, and digoxin) are affected.**
- **Tissue binding is reduced and the V_D of digoxin is decreased by 50% in patients with category 5 CKD, leading to elevated serum concentrations.**
- **In this case, the absolute amount of digoxin bound to the receptor is reduced.**

Pharmacokinetic Changes In CKD

Elimination:

- **Elimination of a drug from the body is expressed as total systemic clearance (CL_T), which is defined as the sum of renal clearance (CL_R) and non-renal clearance CL_{NR}.**

Pharmacokinetic Changes In CKD

Renal Clearance:

- "kidney function" refers to glomerular filtration, tubular secretion, and reabsorption, as well as endocrine and metabolic functions.
- Renal clearance (CL_R) of a drug is the composite of GFR, tubular secretion, and reabsorption ($CL_R = [GFR \times fu] + [CL_{secretion} - CL_{reabsorption}]$), where fu is the fraction of the drug unbound to plasma proteins.

Pharmacokinetic Changes In CKD

- **Several drugs are actively secreted by one or more transporter families:**

1. **Organic cationic transporter(famotidine, trimethoprim, and dopamine).**
2. **Organic anionic transporter (ampicillin, cefazolin, and furosemide)**
3. **Nucleoside transporter (zidovudine)**
4. **P-glycoprotein (Pgp) transporter (digoxin, vinca alkaloids, and steroids).**

Pharmacokinetic Changes In CKD

- **Alterations in filtration, secretion, or reabsorption, secondary to CKD may change drug disposition.**
- **For drugs that are primarily filtered, a reduction in GFR will result in a proportional decrease in renal drug clearance.**

Pharmacokinetic Changes In CKD

Non-renal Clearance:

- CL_{NR} refers to all routes of drug elimination, except renal excretion of unchanged drug.
- It includes hepatic and extrahepatic metabolism and transcellular transport pathways.
- It might be affected by renal disease.

TABLE 9-7 ■ EFFECT OF END-STAGE KIDNEY DISEASE ON NONRENAL OR METABOLIC CLEARANCE OF SELECTED DRUGS[a]

DECREASED			
Acyclovir	Cefsulodin	Imipenem	Procainamide
Aztreonam	Ceftizoxime	Isoniazid	Quinapril
Bufuralol	Cilastatin	Methylprednisolone	Roxithromycin
Captopril	Cimetidine	Metoclopramide	Verapamil
Cefmenoxime	Ciprofloxacin	Minoxidil	Zidovudine
Cefmetazole	Cortisol	Moxalactam	
Cefonicid	Encainide	Nicardipine	
Cefotiam	Guanadrel	Nitrendipine	
Cefotaxime	Erythromycin	Nimodipine	
Increased			
Bumetanide	Fosinopril	Phenytoin	
Cefpiramide	Nifedipine	Sulfadimidine	

[a] An increase or decrease of 40% or greater was considered to be potentially clinically significant.

Pharmacokinetic Changes In CKD

Accumulation of Metabolites:

- **Drugs that are eliminated by glomerular filtration, and given to category 4 & 5 CKD patients may have significant accumulation of parent drug and its metabolite(s).**
- **The accumulation of metabolites and toxic end-products of intermediary metabolism seen in CKD, may affect the disposition of other drugs.**

Pharmacokinetic Changes In CKD

- **Some metabolites may have pharmacologic activity similar to that of the parent drug:**

a. **Oxypurinol is an active metabolite of allopurinol**
b. **Morphine is metabolized to the active metabolites morphine-3- glucuronide and morphine-6-glucuronide which readily cross the blood-brain barrier and bind to opiate receptors, exerting strong analgesic effects.**

Pharmacokinetic Changes In CKD

- **The metabolite may have dissimilar pharmacologic action (norpethidine has CNS stimulatory activity that produces seizures, whereas pethidine has CNS depressant actions).**

Pharmacodynamic Changes In CKD

- **In CKD, the response to a given drug many change beyond that predicted by pharmacokinetic changes alone.**
- **Uremic toxins' accumulation may cause complex disturbances of the coagulation system leading to increased bleeding.**
- **Therefore, enoxaparin dosage adjustment based on creatinine clearance may NOT lead to optimal anticoagulation.**

Estimation of Kidney Function for Drug Dosage Regimen Individualization

- **Accurate assessment of kidney function is needed for appropriate drug dosing regimens.**

Methods:

1. **Accurate measurement of GFR (creatinine clearance) of the patient involved, as you see in the clinical setting.**
2. **Use of equations derived by epidemiological studies. Many of these are available for different populations of patients.**

Estimation of Kidney Function for Drug Dosage Regimen Individualization

- **The Cockcroft Gault (CG) equation for patients over 40 years:**

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{Age}) \times (\text{Weight in kg})}{72 \times \text{Serum creatinine in mg/dL}}$$

- **For women, the result should be multiplied by 0.85 (because of reduced muscle mass).**

Estimation of Kidney Function for Drug Dosage Regimen Individualization

- You should be aware that this equation and other equations are only approximations, and other patient factors should be considered.
- Then, the dose can be calculated according to renal clearance taking into consideration the presence of non-renal clearance of the drug.

$$MD = Cl_D \times \text{Desired } C_{ss}$$

- Or,

$$C_{av}^{\infty} = \frac{FD_0}{V_D k \tau}$$

Relationship Between CL_{cr} and CL of Select Drugs

Drug	Total Body Clearance
Amikacin	CL = 0.6 (CLcr) + 9.6
Gentamicin	CL = 0.983 (CLcr)
Ciprofloxacin	CL = 2.83 (CLcr) + 363
Digoxin	CL = 0.88 (CLcr) + 23
Imipenem	CL = 1.42 (CLcr) + 54
Lithium	CL = 0.20 (CLcr)
Piperacillin	CL = 1.36 (CLcr) + 1.50
Vancomycin	CL = 0.69 (CLcr) + 3.7

Secondary References Used for Drug Dosing in CKD

1. Aronoff's Drug Prescribing in Renal Failure.
2. The Renal Drug Handbook.
3. Lexicomp.
4. Micromedex.
5. American Hospital Formulary Service.
6. Others:

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.

Dosing Adjustments

- **Loading doses usually do not need to be adjusted in patients with chronic kidney disease.**

Dosing Adjustments

Methods for maintenance dosing adjustments:

- Dose reduction, lengthening the dosing interval, or both.

1. Dose reduction involves reducing each dose while maintaining the normal dosing interval.

- This approach maintains more constant drug concentrations, but is associated with a higher risk of toxicities if the dosing interval is inadequate to allow for drug elimination.

Dosing Adjustments

2. **Normal doses are maintained, but the dosing interval is prolonged to allow time for drug elimination before re-dosing.**

- **Prolongation of the dosing interval is associated with a lower risk of toxicities but a higher risk of subtherapeutic drug concentrations, especially toward the end of the dosing interval.**

Select drugs that require renal dosage adjustments:

- Allopurinol
- Lithium
- Acyclovir
- Amantadine
- Fexofenadine
- Gabapentin
- Metoclopramide
- Ranitidine
- Rivaroxaban
- Cephalexin
- Amoxicillin
- Cefuroxime
- Ciprofloxacin
- Clarithromycin
- Levofloxacin
- Nitrofurantoin
- Piperacillin/Tazobactam
- Tetracycline
- Trimethoprim/Sulfamethoxazole

This list is NOT conclusive

Dosing Adjustments

1. Diuretics:

- Thiazide diuretics are considered first-line treatment for patients with uncomplicated hypertension and CKD (only if Scr < 2.5 mg/dL or CrCl > 30 mL/min).
- Loop diuretics are also commonly used to treat uncomplicated hypertension in CKD patients.
- Potassium-sparing diuretics should be avoided because potassium is dangerous to these patients.

Dosing Adjustments

2. **Antihypertensives:**

- **Angiotensin-conver ting enzyme inhibitors and angiotensin receptor blockers are first-line antihypertensives used in patients with type 1 or 2 diabetes and early CKD.**
- **Hydrophilic β-blockers (atenolol, bisoprolol, and nadolol) require dosing adjustments in CKD patients.**

Dosing Adjustments

3. Antihyperglycemic Agents:

- A renally-excreted agent like metformin is not recommended if Scr is >1.5 mg/dL in men or >1.4 mg/dL in women.
- It is important to monitor CKD patients on metformin closely for lactic acidosis development.
- Sulfonylureas (chlorpropamide and glyburide) should be avoided in patients with stage 3 - 5 CKD, as their use increases hypoglycemia risk.

Dosing Adjustments

4. Analgesics:

- **Metabolites** of **morphine, tramadol, and codeine** can accumulate in CKD patients, leading to respiratory depression.
- Dosage reduction is recommended for morphine and codeine in patients with CrCl < 50 mL/min.
- Metabolite accumulation can lead to supra-therapeutic concentrations and cause toxicity.
- Dosing intervals for opioids may need to be modified in CKD patients.

Dosing Adjustments

5. Statins:

- Statin therapy for dyslipidemia is commonly used in CKD patients.

a. Atorvastatin has no dose adjustment recommendation.
b. Rosuvastatin, simvastatin, and lovastatin need dose adjustment
c. Fluvastatin should be used with caution in CKD patients.

Dosing Adjustments

- The following slides might be used as resource information for dose adjustment in CKD.

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.

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.

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

		Dosage adjustment (percentage of usual dosage) based on GFR (mL per minute per 1.73 m²)		
Drug	*Usual dosage*	*> 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				

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
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 m²)		
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.