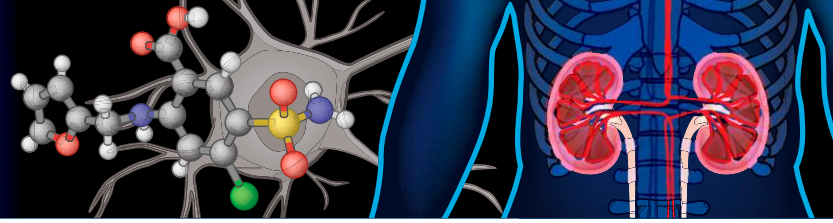
Nephropharmacology
for the Clinician



Clinical Pharmacology of Antibiotics

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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.

CJASN 14: 1080–1090, 2019. doi: https://doi.org/10.2215/CJN.08140718

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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

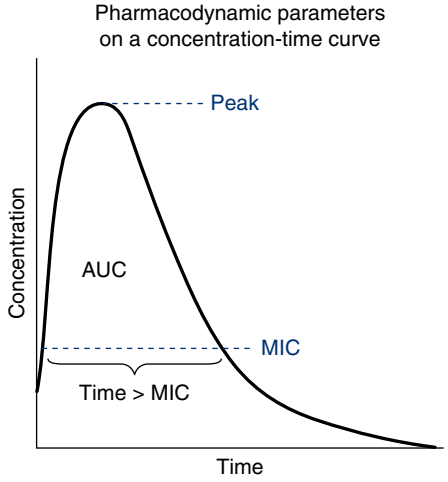

Figure 1. | Pharmacodynamic parameters on a concentration–time curve. Peak:MIC is the parameter to optimize for concentration-dependent antibiotics. Time>MIC is the parameter to optimize for time-dependent antibiotics.

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.

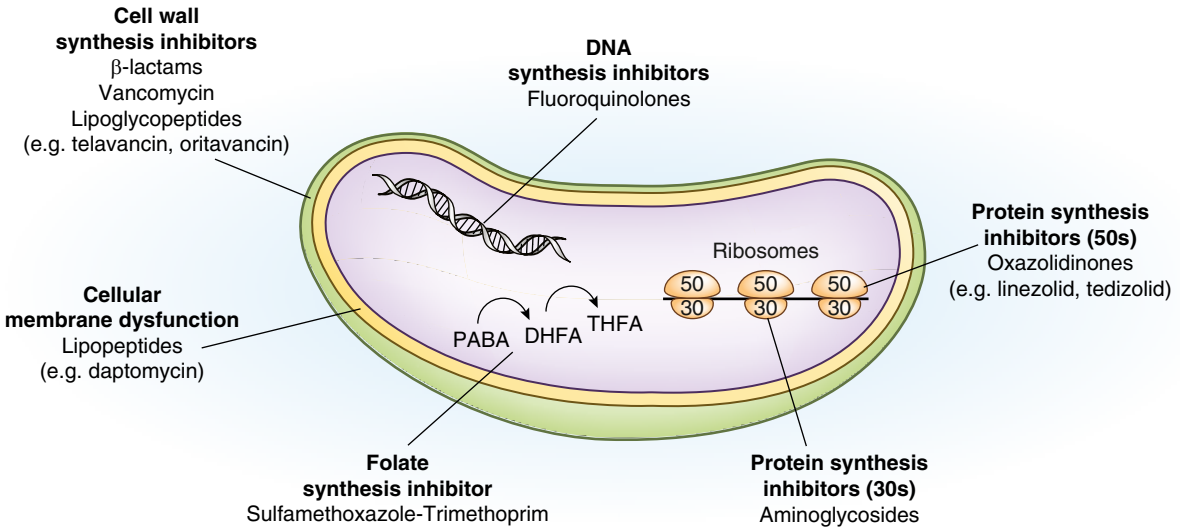

Figure 2. | **Mechanisms of antibiotic classes.**

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)	
		Bacteroides fragilis ++ (M)	
Sulfamethoxazole-trimethoprim	MSSA/MRSA +++	*Escherichia coli* ++	Skin/soft tissue infections
	Staphylococcus epidermidis +++	ESBL *Escherichia coli* ++	Urinary tract infections
	Streptococcus pyogenes +++	*Klebsiella sp.* ++	Pyelonephritis
	Streptococcus pneumoniae +	*Serratia* sp. ++	*Pneumocystis* pneumonia
		Proteus sp. ++	Upper respiratory tract infections

++, 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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Published online ahead of print. Publication date available at www.cjasn.org.