Urinary tract infections (UTIs) are common in small animal practice; it has been reported that up to 27% of dogs will develop infection at some time in their lives.¹

Most UTIs are successfully treated with commonly used drugs, dosages, and administration intervals. However, infections can be challenging to effectively treat when they involve the kidneys (pyelonephritis) and prostate (prostatitis). In addition, it can be difficult to create an appropriate antibiotic prescription in patients with kidney disease due to reduced drug clearance.

Understanding drug pharmacokinetics (PK) and pharmacodynamics (PD) is essential when determining the most effective antibiotic therapy. In addition, successful antimicrobial therapy requires appropriate choice of antibiotic, including dose, frequency, and duration (Figure 1).

PATHOPHYSIOLOGY OF UTI

Nearly all infections are caused by pathogenic bacteria, although fungal or viral UTIs may be rarely encountered. Most bacterial lower UTIs result from bacteria ascending the external genitalia and urethra. Less commonly, bacteria travel hematogenously and colonize the urinary tract.

Numerous innate defense mechanisms help prevent a UTI. Complete and regular voiding, along with intrinsic properties of urine (high osmolality, antimicrobial solutes), helps create a hostile environment for microbes within the urinary tract. Anatomic barriers and mucosal defenses further prevent adherence of virulent bacteria to the urothelium.

Pathogenic bacteria increase the permeability of the urothelium, allowing passage of inflammatory solutes

### Signs of UTI
- Dysuria
- Hematuria
- Pollakiuria
- Stranguria
FIGURE 1. Algorithm that provides guidance on appropriate selection of an antibiotic for urinary tract infection. MIC = minimum inhibitory concentration; UTI = urinary tract infection.
into the subepithelium as well as inflammatory cytokine secretion. The result is inflammation and pain, which manifest as dysuria, pollakiuria, stranguria, and/or hematuria. Eradication of the virulent organism can allow the normal permeability and integrity of the urothelium to be restored.

**CLASSIFICATION OF UTI**

There are several classifications of UTI:

- **Uncomplicated UTI** is a sporadic bacterial cystitis found in a healthy patient with normal urinary tract anatomy and function.

- **Complicated UTI** occurs in a patient with functional or anatomic abnormalities of the urinary tract, or in patients with risk factors for persistent or recurrent infection as well as treatment failure. Such conditions include immunosuppression (due to natural disease or prescribed therapy), diabetes mellitus, hyperadrenocorticism, kidney disease, prostatitis, pregnancy, urinary incontinence, and altered neurogenic function of the bladder.

- **Recurrent UTI** requires investigation to determine whether it is reinfection, relapsing, or refractory.

Reinfection is the return of a UTI—caused by a different organism—within 6 months of discontinuation of antibiotic therapy.

Relapsing UTI occurs when the same organism is cultured again within 6 months of discontinuation of antibiotic therapy. This suggests that the patient has a condition that allows recolonization or one that prevents total eradication of infection; additional diagnostics are warranted in these patients (Table 1).

Refactory UTI occurs when a positive urine culture is obtained during appropriate antibiotic therapy (based on in vitro susceptibility testing). There are several possible causes for refractory UTI, including:

- Decreased renal drug elimination (results in lower than expected urine drug concentration)

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**TABLE 1 Relapsing Urinary Tract Infections: Causes & Diagnostics**

<table>
<thead>
<tr>
<th>CAUSES</th>
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</thead>
<tbody>
<tr>
<td>Functional or structural abnormalities of the urinary tract that allow for recolonization of bacteria, including:</td>
<td></td>
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<tr>
<td>Urinary or fecal incontinence</td>
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<tr>
<td>Recessed vulva</td>
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<tr>
<td>Incomplete bladder emptying</td>
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<tr>
<td>Vaginal urine pooling</td>
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<tr>
<td>Internal nidus that bacteria can colonize, preventing complete eradication, such as:</td>
<td></td>
</tr>
<tr>
<td>Neoplasia</td>
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<tr>
<td>Uroliths</td>
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<tr>
<td>Foreign material</td>
<td></td>
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<tr>
<td>Altered immune function that creates difficulty in curing UTI, particularly when bacteriostatic drugs are used as therapy; such conditions include:</td>
<td></td>
</tr>
<tr>
<td>Hyperadrenocorticism</td>
<td></td>
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<tr>
<td>Diabetes mellitus</td>
<td></td>
</tr>
<tr>
<td>Systemic or local neoplasia</td>
<td></td>
</tr>
<tr>
<td>Administration of immunosuppressive drugs and chemotherapy</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>DIAGNOSTICS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal ultrasonography</td>
<td></td>
</tr>
<tr>
<td>Computed tomography</td>
<td></td>
</tr>
<tr>
<td>Cystoscopy</td>
<td></td>
</tr>
<tr>
<td>Endocrine testing</td>
<td></td>
</tr>
<tr>
<td>Thoracic radiography</td>
<td></td>
</tr>
<tr>
<td>Urinary contrast study</td>
<td></td>
</tr>
</tbody>
</table>

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**CLSI Classification**

Isolate classifications—susceptible, intermediate, or resistant—are established by the Clinical Laboratory Standards Institute (CLSI) on the basis of drug PK and PD data. Several factors are considered in the establishment of CLSI breakpoint classifications.

The peak drug concentration ($C_{\text{max}}$) obtained by a standard dose and normal route of administration must be higher than the isolate’s minimum inhibitory concentration (MIC) for the isolate to be labeled susceptible. The $C_{\text{max}}$ is not always based on the drug concentration in urine. Some drugs have established CLSI breakpoints for UTI in some bacterial species (see CLSI publication VET01S); other breakpoints are based on infection in other organ systems or are even extrapolated from human use.

Drugs for which no breakpoint has been determined for UTI may still be effective against “intermediate” organisms because the concentration of the drug in urine may be higher than in plasma. When urine culture and susceptibility results are used to choose appropriate therapy for pyelonephritis, the plasma breakpoints should be used, rather than urine breakpoints.

All of the preceding factors should be considered in selecting the most appropriate drug, as well as dosage and frequency of administration.
• Inappropriate drug dose or administration schedule
• Low drug bioavailability (e.g., due to drug compounding or gastrointestinal disease)
• Poor drug compliance

Additionally, some drugs may show efficacy \textit{in vitro}, but, for unknown reasons, the same effect is not present \textit{in vivo}.

**DIAGNOSTICS & DATA FOR ANTIBIOTIC SELECTION**

Pharmacokinetics & Pharmacodynamics

PK is the \textit{movement of a drug throughout the body} and includes absorption, distribution, metabolism, and excretion. PD is the \textit{effect of the drug on the body}; in the case of antibiotics, this also includes the effect on the microorganism. These relationships, often referred to as PK/PD, help predict the outcome of any drug prescription.

Alterations in PK may happen with abnormal absorption (e.g., severe gastrointestinal disease), drug metabolism (e.g., synthetic liver dysfunction), altered protein binding (e.g., uremia, hypoproteinemia), and diminished drug excretion (hepatic or kidney failure). An antibiotic’s PD is assessed clinically through \textit{in vitro} culture and susceptibility testing.

Culture & Sensitivity

Ideally, all patients with a suspected UTI should have a urine sample collected via cystocentesis and evaluated by aerobic culture and antibiotic susceptibility testing. Urine culture is considered the gold standard in the diagnosis of UTI.

The 2 techniques for determining antibiotic susceptibility are the disk diffusion and serial dilution methods. \textit{Disk diffusion testing} is considered less reliable and does not provide the minimum inhibitory concentration (MIC) of the antibiotic, whereas \textit{antimicrobial dilution} does provide the MIC and is the preferred method of antibiotic susceptibility testing.

With antimicrobial dilution, a concentration of an antibiotic is added to a liquid medium inoculated with the bacterial isolate. The concentration of antibiotic is doubled in each subsequent well. The MIC is the concentration of antibiotic found in the first tube that exhibits no detectable growth, and this concentration is used to categorize the isolate as \textit{susceptible}, \textit{intermediate}, or \textit{resistant} (see \textit{CLSI Classification}).

Rarely, false-negative findings may result from inappropriate urine storage or slow organism growth (as seen with \textit{Corynebacterium} species). Urine processing for quantitative culture should be performed immediately after urine is obtained because bacterial colony count dramatically drops after 24 hours of refrigerated storage when urine is stored in a silicone clot tube. If urine cannot be processed for quantitative culture immediately, use of a urine transport tube is recommended to help prevent false-negative or underestimated colony count results.

**Urine Drug Concentration**

Many antibiotics are excreted primarily in urine and achieve concentrations substantially higher than those in plasma. The urine drug concentration should be evaluated with respect to the isolate’s MIC to determine the likelihood of eliminating the organism. Table 2 lists observed urine concentration of antibiotics at the specified dosages in healthy animals.

Urine antibiotic concentrations in veterinary patients with kidney disease have yet to be investigated. Reduced glomerular filtration rate (GFR) may decrease the excretion of the drug into urine, resulting in decreased urine concentrations. Additionally, polyuric patients may experience further reduction of urine drug concentration because of increased daily urine volume and subsequent dilution of filtered antibiotic.

Decreased urine excretion caused by diminished GFR can result in plasma drug concentrations exceeding those normally observed and may cause adverse effects. This is most true for drugs with significant kidney elimination. Drugs with mostly
hepatic elimination may have minimal alteration in drug excretion in patients with decreased GFR. However, the accumulated uremic toxins and hypoproteinemia present in many patients with kidney disease can lead to altered drug protein binding and abnormal drug PK/PD.

**ANTIBIOTIC SELECTION BY UTI CLASSIFICATION**

**Empiric Antibiotic Selection**

The emergence of antimicrobial resistance and multidrug resistance has increased, making empiric antibiotic selection very difficult, particularly when previous antibiotic therapy has been administered to the patient.4

**Uncomplicated UTI**

Recommended drugs for uncomplicated UTI include amoxicillin, cephalosporins, and trimethoprim-sulfonamide.5,6 Although patients with an uncomplicated UTI are often successfully treated empirically, repeated treatment without culture and susceptibility results may lead to incorrect choice of antimicrobial, unnecessary adverse effects, and potential selection of resistant bacteria.4

**Complicated & Recurrent UTI**

Antibiotics should never be selected empirically for complicated UTI without culture susceptibility results (see Culture & Sensitivity). Management of pyelonephritis, prostatitis, and relapsing or recurrent

### TABLE 2 Antibiotics for Urinary Tract Infections, including Mean Urine Drug Concentrations7,9

<table>
<thead>
<tr>
<th>DRUG</th>
<th>DOSAGE &amp; ROUTE</th>
<th>MEAN URINE CONCENTRATION (MCG/ML)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>5 mg/kg SC q24h</td>
<td>342 ± 143</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>11 mg/kg PO q8h</td>
<td>202 ± 93</td>
</tr>
<tr>
<td>Amoxicillin/clavulanate</td>
<td>12.5 mg/kg PO q8h</td>
<td>201</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>26 mg/kg PO q8h</td>
<td>309 ± 55</td>
</tr>
<tr>
<td>Cefovecin</td>
<td>8 mg/kg SC q15d</td>
<td>9 ± 6.5 (12 h post) 0.9 ± 0.7 (15 d post) 66 ± 37 (12 h post) 3 ± 1.6 (15 d post)</td>
</tr>
<tr>
<td>Cephalexin</td>
<td>18 mg/kg PO</td>
<td>500</td>
</tr>
<tr>
<td></td>
<td>30 mg/kg PO q8h</td>
<td>225</td>
</tr>
<tr>
<td>Chloramphenicol</td>
<td>35 mg/kg PO q8h</td>
<td>124 ± 40</td>
</tr>
<tr>
<td>Doxycycline</td>
<td>5 mg/kg PO q12h</td>
<td>53 ± 24</td>
</tr>
<tr>
<td>Enrofloxacin</td>
<td>5 mg/kg PO q24h</td>
<td>40 ± 10</td>
</tr>
<tr>
<td>Marbofloxacin</td>
<td>2.75 mg/kg PO</td>
<td>14</td>
</tr>
<tr>
<td>Meropenem</td>
<td>20 mg/kg IV or SC</td>
<td>1296</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>4.4 mg/kg PO q8h</td>
<td>100</td>
</tr>
<tr>
<td>Sulfisoxazole</td>
<td>22 mg/kg PO q8h</td>
<td>1466 ± 832</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>18 mg/kg PO q8h</td>
<td>139 ± 65</td>
</tr>
<tr>
<td></td>
<td>20 mg/kg PO q8h</td>
<td>145 ± 39</td>
</tr>
<tr>
<td>Trimethoprim/sulfadiazine</td>
<td>15 mg/kg PO q12h</td>
<td>55 ± 19</td>
</tr>
</tbody>
</table>
UTI is often unsuccessful without therapy guided by culture and susceptibility results. However, therapy should be instituted while culture and susceptibility results are being awaited. Rational initial drug choices for complicated UTI include amoxicillin, fluoroquinolones, or trimethoprim-sulfonamide.

**ANTIBIOTIC SELECTION BY URINE DRUG CONCENTRATION**

To best use antibiotic urine data, an important consideration is whether a drug is time- or concentration-dependent.

**Time-Dependent Drugs**

Time-dependent drugs include beta-lactams, cephalosporins, sulfa drugs, tetracyclines, and chloramphenicol. These drug classes are most effective when the tissue concentration exceeds the isolate’s MIC for 50% to 75% of the dosing interval. However, few clinical trials have evaluated this suggestion.

Product inserts and pharmacology texts often contain the drug elimination curves, which are helpful in choosing the dosage and frequency that ensure these criteria are met. The plasma drug elimination curve and renal drug elimination rate can be used as surrogates to predict the urine drug concentration curve.

Less is known about urine drug concentration and clinical efficacy, but several authors have stated that urine, not plasma, drug concentration is important in ensuring successful eradication of bacteria (see Urine Drug Concentration & Clinical Efficacy).

**Concentration-Dependent Antibiotics**

The efficacy of concentration-dependent antibiotics is best predicted by the $C_{\text{max}}$ and the isolate’s MIC. Such drugs as fluoroquinolones and aminoglycosides are most effective when the $C_{\text{max}}$ is at least 8- to 10-fold higher than the MIC. These drugs are typically administered every 24 hours.

Another method to evaluate the activity of these antibiotics is comparing the drug concentration area under the curve (AUC) to the MIC. This AUC/MIC ratio has been investigated for some antibiotics, and although some authors generally recommend an AUC/MIC greater than 125 to 250, studies have shown some drugs to be effective with an AUC/MIC of 40.

The dosage of these antibiotics is typically chosen to create a high peak urine concentration, well above the isolate’s MIC. Once-daily administration is acceptable for most concentration-dependent drugs, and this frequency may help increase owner compliance in administering medications. However, it may not be consistent with antibiotic stewardship to prescribe a fluoroquinolone antibiotic for an uncomplicated lower UTI when drugs belonging to the penicillin or cephalosporin class would also be effective.

**DURATION OF THERAPY**

The ideal duration of antibiotic therapy for uncomplicated and complicated UTI is unknown. Many textbooks recommend 10 to 14 days for uncomplicated UTI and 4 to 8 weeks for complicated UTI; however, these guidelines are
FOCUS ON PHARMACOLOGY

not evidence-based, and much shorter durations are the standard of care in human medicine.

In 2011, the International Society for Companion Animal Infectious Diseases published recommendations regarding antimicrobial therapy in UTI. The recommendations mostly reflect expert consensus because well-designed clinical trials to determine optimal antibiotic duration are lacking in veterinary medicine.

- For uncomplicated UTI, this group recommended 7 or fewer days of antibiotic therapy; humans are typically treated for 3 to 7 days.
- For complicated UTI, the group recommended antibiotic therapy for up to 4 weeks; humans are typically treated for 1 to 2 weeks, although 3 weeks may be indicated in some instances.

Recently, 2 studies evaluated short duration versus long duration of antibiotics for uncomplicated UTI in dogs (3 days of trimethoprim-sulfamethoxazole versus 10 days of cephalixin and 3 days of enrofloxacin versus 14 days of amoxicillin-clavulanic acid). Both studies demonstrated that the short duration of antibiotic administration was noninferior to the longer duration in bacterial cure rates. However, because both studies compared short duration of one drug with long duration of another, their design precludes determination of optimal treatment time for the drugs investigated.

A systematic literature review conducted in 2015 to determine the optimal therapy for UTI in veterinary medicine found insufficient evidence available for analysis. Currently, evidence-based guidelines for the duration of UTI in small animals do not exist, and further studies evaluating a single drug in both short and long durations of therapy are needed.

MONITORING RESPONSE TO THERAPY

Patients with a simple, uncomplicated UTI may not require rigorous monitoring. However, patients with complicated, relapsing, or recurrent infections should be monitored very closely. The following protocol is recommended to monitor response to therapy in patients with relapsing, recurrent, or refractory UTI.

Urine Drug Concentration & Clinical Efficacy

Antimicrobial drugs must achieve an adequate urine concentration, which must be maintained for a sufficient time for a drug to be effective in treating UTI. It has been suggested that clinical efficacy is observed when the urine drug concentration is maintained at a concentration 4-fold higher than the isolate’s MIC throughout the time between doses. Experimental studies in rats have shown that the time for which the plasma drug concentration exceeds the isolate’s MIC correlates to the magnitude of bacterial colony count reduction; the longer the time for which the drug concentration remained above the MIC, the lower the urine colony counts. Successful eradication of bacteria within the renal parenchyma or urinary bladder wall is correlated to the plasma, not urine, drug concentration.

When prescribing time-dependent antibiotics, shortening the interval between drug administration is the most effective method to allow the tissue/urine drug concentration to exceed the MIC for the majority of the dosing interval.

- Drug elimination follows first-order kinetics, where 50% of the drug is lost in 1 half-life.
- In contrast, doubling the dose would only add 1 half-life to the dosing interval.
- To add 2 half-lives to the dosing interval, the initial dose would have to be increased 4-fold. The peak serum drug concentration achieved by this approach may exceed the window of safety, producing adverse drug effects.

For example, amoxicillin could be administered to dogs at a dosage of 10 to 20 mg/kg q12h; however, to maintain higher drug concentrations, the same dose could be administered q8h.

One method to ensure that the tissue or plasma drug concentration consistently exceeds the MIC is to deliver the antibiotic as a continuous IV infusion. This may be particularly useful in critically ill animals, such as those with urosepsis or those that have an impaired immune response.

1. Recheck urine culture 5 to 7 days into antibiotic therapy. This confirms that the prescribed dose and frequency of the drug were successful in treating the organism isolated. This culture also may reveal an additional isolate that could not be identified in the initial culture. Any bacterial growth observed at this time suggests treatment failure. Reconsider the choice of antibiotic, dose, and administration frequency.

2. Recheck urine culture 3 days before discontinuing antibiotic therapy. This is an
optional step, but it confirms that, when therapy was discontinued, the patient still had a negative culture. Positive bacterial growth at this stage suggests a refractory infection or newly inoculated organism. Investigate patients for any nidus of infection (eg, urolithiasis, anatomic abnormality, local neoplasia). Alter treatment and institute new therapy for the same duration as previously intended.

3. Recheck urine culture 7 days after discontinuing antibiotic therapy. Positive growth should prompt investigation for causes of relapse or reinfection.

Complicated, relapsing, recurrent, and refractory UTI may be challenging to cure. However, understanding drug PK/PD and potential alterations in the animal’s metabolism/excretion of the drug can help increase the likelihood of successful treatment.

IN SUMMARY

Guidelines for appropriate antibiotic dosing for animals with kidney disease have not been established; therefore, a working knowledge of pharmacology and the prescribed drug’s PK/PD profile is needed to help create a successful antibiotic prescription with the smallest risk for adverse effects.

When possible, in patients with kidney disease, avoid drugs that have a narrow margin of safety and undergo significant renal elimination (eg, fluoroquinolones in cats, aminoglycosides) and then choose alternative drugs (based on susceptibility results) that undergo hepatic elimination or those with a wide margin of safety. TVP

References

Author’s Note

The lack of data and the limitations in well-designed studies prevent complete evidence-based guidelines from being described for treatment of urinary tract infection (UTI). This article presents an approachable and logical process for treating UTI; however, it too lacks clinical validation.

The usefulness of urine drug concentrations has been debated, but several textbooks and peer-reviewed manuscripts suggest that these concentrations can play a role in creating a valid antimicrobial drug prescription. In addition, while the clinical success of drug therapy cannot be predicted on urine drug concentration alone, in the absence of individual patient drug therapeutic monitoring, glomerular filtration rate testing, and urine drug bactericidal assessment data, there are few hard facts on which to base therapy.

This article focuses on relevant topics in drug pharmacokinetics/pharmacodynamics, urine susceptibility testing, and educated drug therapy, and numerous holes in our understanding prevent these topics from being without question or debate. However, I hope this article helps increase the understanding of drug pharmacology, where it pertains to UTI, to the best of our understanding.

—JD Foster, VMD, DACVIM


**Glossary**

- **AUC**: area under the curve
- **CLSI**: Clinical Laboratory Standards Institute
- **Cmax**: peak drug concentration
- **GFR**: glomerular filtration rate
- **MIC**: minimum inhibitory concentration
- **PD**: pharmacodynamics
- **PK**: pharmacokinetics
- **UTI**: urinary tract infection

**JD Foster**

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