ISCAID Consensus Statement: Antimicrobial Guidelines for the Treatment of Urinary Tract Infections in Dogs and Cats

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Introduction

Urinary tract disease is frequently encountered in dogs and cats and is a common reason for antimicrobial therapy. In humans, concerted efforts are underway to improve and limit antimicrobial use because of concerns regarding overuse, misuse, and ineffective use.[1-3] Some of these same issues have been identified in veterinary medicine, leading to development of clinical guidelines for diagnosis and management of urinary tract infections in dogs and cats.[4] As the field has advanced, more companion animal-specific research has been published.[5-7] Feedback was also obtained from users. It became clear that these guidelines needed to evolve; therefore, the process of revising of the 2011 ISCAID guidelines was initiated in 2015. As with any clinical guideline, these guidelines are designed to provide 'guidance,' not dictate a standard of care that must apply to all situations. They are based on evidence, whenever applicable, but the paucity of high level evidence in veterinary medicine results in the need for extrapolation from human medicine and the use of personal opinions from an expert panel.

Scope

The revised guidelines expand on the 2011 version both in terms of specific recommendations, as well as in scope and depth. It was realized that defining of some patient/disease categories was difficult (or difficult to justify) and that extrapolation of some definitions from human medicine was problematic. For example, 'uncomplicated' or 'simple uncomplicated UTI' are common categorizations in humans.[8] While it is based on the presence of UTI in an individual with a normal urogenital tract, specific testing is rarely performed and this population consists predominantly of young, otherwise healthy sexually active women. Therefore, this is not analogous to most UTIs in female dogs. Infections in men are typically considered complicated, something that would reasonably apply to intact male dogs; however, intact males constitute a great minority of dogs in many regions. Recurrent disease is a common problem in companion animals, and the reasons can be diverse. Differentiating a new infection caused by an unaddressed predisposing factor (e.g., anatomical abnormality, immune suppression, neurogenic bladder) from an infection that was not completely

eliminated (e.g., urolith, bladder wall mass, poor owner compliance with antimicrobials) is important, and detailed consideration of what 'recurrent' means is required to properly diagnose and manage these complicated cases. There are also important subpopulations that have specific facets that necessitate additional or different approaches to diagnosis and treatment, including pregnant bitches, intact male dogs, and individuals with urologic implants, urinary catheter or uroliths. Further, advances in interest and study of a range of alternative or complementary approaches to the management of UTIs, particularly recurrent UTIs, necessitate specific consideration of these non-antimicrobial therapies.

As such, the following conditions or topics have been addressed, attempting to separate topics with important clinical differences and improve on existing (and often unclear) definitions:

- First episode urinary tract infection in the female and neutered male dogs
- First episode urinary tract infection in the cat
- First episode urinary tract infection in the intact male dog
- Recurrent bacterial urinary tract infection
- Pyelonephritis
- Bacterial prostatitis
- Bacterial UTI in the pregnant bitch
- Subclinical bacteriuria
- Bacteriuria, infection and management of urinary catheters
- Perioperative prophylaxis for urological surgery and minimally invasive urological procedures
- Prophylaxis and treatment of UTI/bacteriuria in animals with urologic implants
- Medical management of infection-induced uroliths
- Non-antimicrobial therapies
- Interpretation of culture and susceptibility tests for treating urinary tract infections

Discussion of these topics is well beyond what can be presented in these proceedings; however, general drug dosing regimens are presented in Table 1.

Drug Treatment Table

Table 1. Antimicrobial recommendations for treatment of urinary tract infections in dogs and cats

Drug	Dose	Comments
Amoxicillin	11–15 mg/kg PO q12h	Good first-line option for bacterial cystitis in the absence of significant tissue involvement (e.g., prostatitis, pyelonephritis). Excreted in urine predominantly in active form if normal kidney function is present.

Amikacin	Dogs: 15–30 mg/kg IV/IM/SC q24h Cats: 10–14 mg/kg IV/IM/SC q24h	Not recommended for routine use but may be useful for treatment of multidrug-resistant organisms. Potentially nephrotoxic. Avoid in animals with chronic kidney disease. Other factors (e.g., low pH) can affect aminoglycoside activity, which should be considered.
Amoxicillin/clavulanate	12.5–25 mg/kg PO q12h (dose based on combination of amoxicillin + clavulanate	First-line option for bacterial cystitis in the absence of significant tissue involvement (e.g., prostatitis, pyelonephritis).
Ampicillin		Not recommended because of poor oral bioavailability. Amoxicillin is preferred.
Cephalexin, cefadroxil	12–25 mg/kg PO q12h	Enterococci are resistant. Limited activity against Enterobacteriaceae.
Cefovecin	8 mg/kg single SC injection. Can be repeated once after 7–14 days.	Duration is longer than is typically needed. Should only be used in situations where oral treatment is problematic. Enterococci are resistant. Approved for treatment of cystitis in some countries, but limited efficacy against Enterobacteriaceae apart from cystitis. Lack of clinical breakpoints hampers assessment of susceptibility, especially in tissue-associated infections.
Cefpodoxime proxetil	Dogs: 5 to 10 mg/kg q24h PO Cats: no dose established.	More active than cephalexin or cefadroxil against Enterobacteriaceae. Enterococci are resistant.
Ceftiofur	Dogs: 2 mg/kg q12–24h SC Cats: no dose established.	Approved for treatment of UTIs in dogs in some regions. Enterococci are resistant
Chloramphenicol	Dogs: 40–50 mg/kg PO q8h Cats: 12.5–20 mg/kg PO q12h	Reserved for rare situations with multidrug-resistant infections having few other treatment options. Myelosuppression can occur, particularly with long-term (e.g., > 28d) therapy. Inhibits metabolism of some drugs. Avoid contact by humans because of rare idiosyncratic aplastic anemia.
Ciprofloxacin	30 mg/kg PO q24h	Difficult to justify over approved fluoroquinolones. Lower and more variable oral bioavailability than approved veterinary fluoroquinolones. Sometimes used because of lower cost than enrofloxacin. Dosing recommendations are empirical and based on limited pharmacokinetic studies. Human breakpoints do not apply: no interpretive criteria are available for testing isolates from animals.

Doxycycline	5 mg/kg PO q12h	Reserved for infections caused by pathogens that are resistant to drugs that are actively excreted in urine in active form.
Enrofloxacin	5–20 mg/kg q24h (dogs)	Excreted in urine predominantly in active form. Reserve for documented resistant cystitis but good first-line choice for pyelonephritis in dogs at the higher end of the dosing range. Considered first-line choice for infections that involve the prostate. Dosing should consider the bacterium and degree of tissue involvement. Lower doses should be avoided in complicated or tissue-associated infections and with certain pathogens (e.g., *Pseudomonas*). Not recommended for enterococci. Not recommended for cats because of the risk of retinopathy at high doses and resistance emergence at lower doses.
Imipenem-cilastatin	5 mg/kg IV/IM q6–8h	Reserve for treatment of multidrug-resistant infections, particularly those caused by ESBL-producing Enterobacteriaceae or *Pseudomonas aeruginosa*. Recommend consultation with a urinary or infectious disease veterinary specialist or veterinary clinical pharmacologist prior to use.
Marbofloxacin	2.7–5.5 mg/kg PO q24h	Excreted in urine predominantly in active form. Reserve for documented resistant cystitis but good first-line choice for pyelonephritis at the higher end of the dosing range. Considered first-line choice for infections that involve the prostate. Dosing should consider the bacterium and degree of tissue involvement. Lower doses should be avoided in complicated or tissue-associated infections and with certain pathogens (e.g., *Pseudomonas*). Not recommended for enterococci.
Meropenem	Dogs: 8.5 mg/kg SC/IV q 12 (SC) or 8 (IV) h Cats: 10 mg/kg q12h, IV, SC, IM.	Reserve for treatment of multidrug- resistant infections, particularly those caused by ESBL-producing Enterobacteriaceae or *Pseudomonas aeruginosa*. Recommend consultation with a urinary or infectious disease veterinary specialist or veterinary clinical pharmacologist prior to use.
Nitrofurantoin	4.4–5 mg/kg PO q8h	An option for some cases of cystitis, particularly when multidrug-resistant pathogens are involved. Not appropriate for tissue-associated infections.
Orbifloxacin	Tablets: 2.5–7.5 mg/kg PO once daily Suspension (cats): 7.5 mg/kg once daily.	Excreted in urine predominantly in active form. Reserve for documented resistant cystitis but good first-line choice for pyelonephritis at the higher end of the dosing range. Considered first-line choice for infections that involve the prostate. Dosing should consider the bacterium and degree of tissue involvement. Lower doses should be avoided in complicated or tissue-associated infections and with certain pathogens (e.g., *Pseudomonas*). Not recommended for enterococci.

Trimethoprim-sulfadiazine/trimethoprim-sulfamethoxazole/ormetoprim-sulfadimethoxine	15–30 mg/kg PO q12h Note: dosing is based on total trimethoprim + sulfadiazine concentration	Concerns regarding idiosyncratic and immune-mediated adverse effects in some patients, especially dogs and with prolonged therapy. If prolonged (> 7d) therapy is anticipated, baseline Schirmer's tear testing is recommended, with periodic reevaluation and owner monitoring for ocular discharge. Avoid in dogs that may be sensitive to potential adverse effects such as KCS, hepatopathy, hypersensitivity, and skin eruptions. Activity against *Enterococcus* in urine is controversial and should be avoided. Trimethoprim can be considered a treatment choice for prostate infections in male dogs. Susceptibility testing is based on trimethoprim-sulfamethoxazole and breakpoints have not been established for dogs or cats.
Fosfomycin	40 mg/kg PO (with food) q12h	Should be reserved for multidrug-resistant infections. Not appropriate for tissue-associated infections. Efficacy in dogs or cats is undetermined.
Pradofloxacin	Dogs: 3–5 mg/kg PO once daily. Cats: 3–5 mg/kg once daily (tablets) or 5–7.5 mg/kg once daily (suspension)	Excreted in urine predominantly in active form. Reserve for documented resistant cystitis but good first-line choice for pyelonephritis at the higher end of the dosing range. Considered first-line choice for infections that involve the prostate. Dosing should consider the bacterium and degree of tissue involvement. Lower doses should be avoided in complicated or tissue-associated infections and with certain pathogens (e.g. *Pseudomonas*). Not recommended for enterococci. Greater activity against some bacteria than older fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin). Approved for dogs and cats in Europe and Canada. Approved only for cats in the U.S. (liquid suspension). Published evidence for efficacy treating UTI in dogs and cats.
Minocycline	Cats: 8.8 mg/kg PO q24h, (or 50 mg per cat). Dogs: 5 mg/kg PO q12h.	Reserved for infections caused by pathogens that are resistant to drugs that are actively excreted in urine in active form. Can be considered an alternative to doxycycline when doxycycline is not available. Some doxycycline-resistant staphylococci are susceptible. Higher doses (10 mg/kg) can be used in dogs but is more likely to cause vomiting.

Subclinical Bacteriuria

Another important topic is subclinical bacteriuria, one that is receiving increasing attention because of overtreatment in humans and animals. Subclinical bacteriuria is defined as the presence of bacteria in urine as determined by positive bacterial culture from a properly collected urine sample, in the absence of clinical evidence of signs of lower urinary tract disease. Some studies in the veterinary literature use the term 'urinary tract infection' or 'occult infections' in reference to animals with positive bacterial cultures but no clinical signs, this terminology should be avoided. The term bacteriuria has been used to describe cases where bacteria are visible cytologically, irrespective of culture results; however, diagnosis should be based on culture.[4] Cytological evaluation is an important part of urinalysis in animals with suspected urinary tract disease and results must be considered in the context of other data. An increased urine sediment white blood cell count has been associated with increased odds of a positive culture,[9,10] but this has not been a consistent finding[11]. Poor agreement between cytological detection of bacteria and positive urine culture has been reported in dogs.[12,13] Increased urine sediment red blood cell count is also not predictive of positive cultures.[9,10] Thus, cytological data are useful adjunctive data to assess animals with potential urinary tract disease but may not be highly predictive of culture results or infectious disease.

Subclinical bacteriuria is not uncommon, even in individuals with no known predisposing factors. Rates of 2.1–8.9% have been reported in healthy dogs,[10,12-15] with higher rates (15–31%) in groups such as dogs with diabetes, morbidly obese dogs, puppies with parvoviral enteritis, and dogs treated with cyclosporine or glucocorticoids[11,12,16-18]. Study of subclinical bacteriuria has been limited in cats and the prevalence may be lower than reported in dogs, as one study identified bacteriuria in only 0.9% of healthy cats.[19] No evidence of an association between subclinical bacteriuria and risk of development of UTI or other infectious complications has been reported in dogs or cats. A study of healthy female dogs identified bacteriuria in 8.9% and found no association with subsequent UTI development.[15]

In humans, there is abundant support for not treating asymptomatic bacteriuria (the human analogue of subclinical bacteriuria), even in most compromised patients. While bacteriuria rates are high in various populations (e.g., diabetics, the elderly, patients with paralysis), treatment guidelines such as Infectious Diseases Society of America Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults do not recommend treating asymptomatic bacteriuria in almost all patient groups.[20] Exceptions are patients undergoing transurethral resection of the prostate and patients that will be undergoing urologic procedures that result in mucosal bleeding. Screening and treatment of pregnant women is recommended; however, this has recently been questioned because while an association between untreated bacteriuria and pyelonephritis was identified, the low burden of pyelonephritis and potential adverse effects of antimicrobials may not justify universal treatment.[21] Treatment is specifically not recommended for premenopausal, non-pregnant women, those with diabetes, older individuals in the community, elderly institutionalized individuals or individuals with spinal cord injuries.[4] Thus, even in what would be considered high-risk populations, treatment of asymptomatic bacteriuria is discouraged and intensive measures are used to reduce the treatment of asymptomatic bacteriuria.These efforts are typically focused around antimicrobial stewardship from an antimicrobial resistance standpoint, but reduction in unnecessary treatment is also desirable because of cost, adverse effects of antimicrobials, and lack of evidence that treatment improves outcome in almost all patient groups. While treatment might eliminate the current bacteriuria event, recolonization often follows.[22] A systematic review concluded that while bacteriuria may be eliminated in the short term, the effect is not sustained and recolonization is common, leading to no impact on overall morbidity or mortality.[23] Further, two studies have reported significantly higher bacteriuria recurrence rates in women treated for asymptomatic bacteriuria compared to untreated controls.[24,25] Treated women also had higher rates of antimicrobial resistance in *E. coli* isolated from subsequent UTIs.[25]

Summary of Preliminary Recommendations

Diagnosis

1. **Subclinical bacteriuria should be based on identification of bacteria by culture of urine collected via cystocentesis in an animal without clinical signs attributable to UTI. Confirmation of bacteriuria through isolation of the same bacterium in two subsequent samples is a requirement for diagnosis in humans[20] and would be ideal in animals**.

2. **Urine collected via catheter should not be used for diagnosis of subclinical bacteriuria unless there are contraindications to cystocentesis. If urine collected via catheter is used, isolation of the same bacterial species from two sequential samples collected at least one week apart is required**.
3. **Subclinical bacteriuria should never be diagnosed from free-catch urine samples**.
4. **Quantitative culture results cannot differentiate subclinical bacteriuria from UTI**. Heavy growth on quantitative culture data (e.g., >100 000 CFU/ml) can be present in animals with subclinical bacteriuria[9] and there is no evidence that high CFU counts indicate a greater risk of disease development.

Treatment

1. **Treatment of bacteriuria is rarely indicated in animals that have no clinical signs of UTI (e.g., stranguria, hematuria, pollakiuria, dysuria)**.
2. **Treatment of animals with pyuria or other cytological abnormalities but no clinical abnormalities is not recommended**. Previous guidelines supported treatment of animals with no clinical signs but cytological evidence of inflammation (pyuria). However, there is currently no evidence in veterinary medicine that treatment of pyuria is beneficial or that pyuria in the absence of clinical signs represents a relevant disease state, and treatment of pyuria in humans in the absence of clinical evidence of UTI is not recommended.[20]
3. **The presence of a multidrug bacterium should not affect decisions about whether to treat bacteriuria**. Antimicrobial resistance genes are not virulence factors and resistant organisms are not more likely to cause disease than their susceptible counterparts. Anecdotal information suggests that multidrug-resistant organisms will sometimes be replaced with susceptible organisms if treatment is withheld, and then treatment with routine antimicrobials may be more practical if decolonization is desired or if clinical disease develops.
4. **Treatment of bacteriuria caused by multidrug-resistant pathogens for infection control purposes (e.g., to eliminate urine shedding of a possible pathogen) is not recommended**. It is reasonable to assume that the bacterial strain in the bladder is also present in the gastrointestinal tract; therefore, even if bacteria are eliminated from the bladder with antimicrobials, it would likely have limited impact on the overall risk posed by the patient.
5. **Culture of urine from clinically normal animals should not be performed when there would be no indication to treat based on a positive culture result**.
6. **In some circumstances, treatment may be considered if there is concern that there is a particularly high risk of ascending or systemic infection (e.g., immunocompromised patients, patients with underlying renal disease) or that the bladder may be a focus of extra-urinary infection**. Good data are lacking to define high-risk populations and it is likely that there are few animals that fall into this category. Therefore, treatment on the basis of suspected high risk of complications should be used sparingly.

7. **In patients that are unable to display clinical signs of UTI (e.g., spinal injury), a clinical judgment must be made, ensuring that consideration of the need and potential adverse impacts (e.g., adverse effects, antimicrobial resistance) are balanced**. Patients that are unable to display clinical signs of UTI complicate decision-making as determining what represents 'subclinical' is difficult. In those patients, the presence of systemic signs (e.g., fever) and changes in urine appearance and odour (e.g., gross discoloration, malodor) can likely help differentiate infection from subclinical bacteriuria, but clear guidance is lacking.
8. **Treatment of subclinical bacteriuria caused by *Corynebacterium urealyticum* should be considered because of its association with encrusting cystitis**, a condition that is difficult to treat and evidence from humans indicating an increased risk of UTI and obstructive uropathy in transplant patients with *C. urealyticum* bacteriuria.[26]
9. **There is currently no evidence that screening bacterial isolates for urovirulence factors should impact decision-making for subclinical bacteria**.

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