Diagnosis and Treatment of Urinary Tract Infections

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Introduction

Urinary tract disease is commonly in dogs and cats, and a leading reason for antimicrobial use. Proper diagnostic and treatment plans are critical for optimal patient care and prudent (and effective) antimicrobial use. In human medicine, detailed guidelines are available and provide excellent guidance to physicians on management of various infectious diseases, including urinary tract infection. Practice guideline development is a relatively new phenomenon in veterinary medicine and is hampered by a relative lack of adequate research. However, a combination of available data, general principles of infectious diseases and antimicrobial therapy and expert opinion have been used to develop preliminary guidelines for urinary tract infections.[11] All urinary tract infections are not alike, and the approach to diagnosis and management can be different.

Sporadic bacteriuria cystitis

Previous often referred to as 'simple uncomplicated urinary tract infection, sporadic bacteriua cystitis is a more accurate term that highlights the presence of inflammation (as opposed to subclinical bacteriuria) and acknowledges that our understanding of complicating factors may be limited. This category has been previously used to only describe patients that a) that are otherwise healthy non-pregnant females or neutered males; b) with no known urinary tract anatomical and functional abnormalities or relevant comorbidities (e.g. endocrinopathy, spinal disease); and, c) that have had fewer than 3 episodes of known or suspected urinary tract infection in the preceding year. However, patients with urinary tract abnormalities or comorbidities can develop sporadic cystitis and not necessarily be at substantially increased risk for complications or recurrence or have infections that are more difficult to treat. Initial or rare (<3 episodes of cystitis in the preceding year) sporadic cystitis in individuals with urinary tract abnormalities or comorbidities should be approached as is described here. Sporadic cystitis is rare in intact male dogs but should be approached as described here if there is no evidence of concurrent prostatitis.

Diagnosis is based on the presence of clinical signs of lower urinary tract disease and urinalysis, ideally with bacterial culture results. Urine culture is preferred for all cases but empirical therapy in lieu of culture can be justified in dogs with sporadic disease, particularly in animals with limited previous antimicrobial exposure and in situations where the likely pathogens and susceptibility patterns are well known. Diagnosis in cats should be confirmed by aerobic bacterial culture in all cases due to the low likelihood of bacterial disease in cats with clinical signs of lower urinary tract disease

Ideally, specimens for culture should be collected by cystocentesis unless there is a contraindication (which would rarely be present in animals with sporadic bacterial cystitis) or significant difficulties in sample collection (e.g. large morbidly obese dog) are anticipated. Samples should be refrigerated and processed by the diagnostic laboratory within 24h of collection. Culture of voided samples should only be performed when cystocentesis is not possible because of the potential for both false positive and false negative cultures. Voided samples should only be cultured if they are refrigerated and processed by the diagnostic laboratory within a few hours.[12] The level of growth ($\geq$100,000 CFU/ml), bacterial species and whether mixed growth is present are important factors to assess when evaluating any culture results from voided samples.

Clinical signs are a result of inflammation. In dogs, a decision to start antimicrobial therapy while awaiting culture results (if samples are submitted) is reasonable. However, there is evidence from humans that analgesics alone may be as effective as antimicrobials in uncomplicated cases.[13,14] Consideration can be given to prescribing an initial course of analgesics and adding antimicrobials 3-4 days later if clinical signs persist or worsen. Regardless, analgesics should be considered during the initial treatment period to help ameliorate clinical signs. To avoid overtreatment in cats, withholding antimicrobial treatment pending the result of aerobic culture is reasonable, unless there is clear evidence on urine sediment analyses to support bacterial infection.

Optimal empirical choices vary based on the pathogen and resistance patterns in the region. However, amoxicillin is a reasonable first choice in most areas. If amoxicillin without clavulanic acid is not readily available, use of amoxicillin/clavulanic acid is reasonable. Evidence of a need for clavulanic acid is lacking and it may not be necessary, even in infections with beta-lactamase producing bacteria, because of the high amoxicillin concentrations that are achieved in urine. Trimethoprim-sulfonamide is another first tier option but may be associated with greater adverse event concerns and is difficult to recommend over amoxicillin or amoxicillin/clavulanic acid. The recommended duration of therapy is 3-5 days. The short end of that dosing period may be optimal, but veterinary research is currently limited.

There is no indication for measures beyond monitoring of clinical signs. Provided the full course of antimicrobials is administered correctly, there is no evidence that intra- or post-treatment urinalysis or urine culture is indicated in the absence of ongoing clinical signs of cystitis.

Recurrent bacterial cystitis

In human medicine, recurrent bacterial cystitis implies a diagnosis of $\geq$ 3 episodes of recurrent bacterial cystitis in the previous 12 months or 2 or more bladder infections in six months.[15-17] This definition has also been adopted in veterinary medicine. Recurrent cystitis may result from relapsing or persistent infection, or reinfection. Refractory infections are defined when there is no response or incomplete clinical response to a course of treatment.

Since recurrent cystitis is almost always associated with an underlying cause, identification and management of relevant risk factors and comorbidities is critical for longterm success. Repeated antimicrobial administration is unlikely to provide longterm cure and can be associated with antimicrobial resistance, treatment costs and risks of adverse effects of antimicrobials. Contrast imaging or cystoscopy may be considered for refractory clinical recurrent bacterial cystitis cases if biopsy of the bladder mucosa is warranted or to investigate further to underlying comorbidities.

Urine culture, ideally from a sample collected via cystocentesis, should be performed. If the pathogen isolated from a patient with recurrent infections is different from previous organisms isolated, reinfection is likely and efforts should be undertaken to identify and address any predisposing factors. If the same bacterial species (e.g. *E. coli*) is isolated again from a patient with clinical signs of lower urinary tract disease but the isolate has a different antibiogram than a previous isolate, advanced molecular studies would be required to conclusively determine if the patient had a new infection, as opposed to selection of a resistant subpopulation of the initial infection that was never fully eradicated.[18] However, re-infection is likely or at least possible. If the isolate has the same antibiogram as a previous isolate, it is likely that relapsing or persistent infection is present, but advanced molecular studies would still be required to conclusively determine if bacterial species present is identical to that previously isolated.

Previous guidelines supported long durations (4 weeks) of antimicrobials for recurrent cystitis.[11] However, recurrent cystitis encompasses a broad patient range, some that develop repeated and relatively uncomplicated infections that likely respond quickly to antimicrobials and others that have marked bladder pathology that complicates treatment. In human medicine, several studies support short-course therapy for acute and recurrent bacterial cystitis.[15]

If empirical antimicrobials are initially prescribed, drug selection should be approached as for sporadic bacteria cystitis, and re-assessed when culture results are available, considering both in vitro susceptibility and patient response to initial treatment.

Long-term therapy is not automatically warranted for recurrent bacterial cystitis. Short (3-5d) durations should be considered for cases where re-infection seems to be occurring. Longer courses (7-14d) may be reasonable in persistent, and potentially relapsing, infections, if factors that inhibit response to antimicrobials, such as bladder wall invasion, are suspected to be present.

Subclinical Bacteriuria

As noted above, the goal of management is to treat disease. This is not necessarily synonymous with the presence of bacteria in urine. Subclinical bacteriuria is defined as the presence of bacteria in urine as determined by positive bacterial culture from a properly collected (i.e. cystocentesis) urine sample, in the absence of clinical evidence of signs of lower urinary tract 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, with higher rates (15-31%) in groups such as dogs with diabetes mellitus, morbidly obese dogs, puppies with parvoviral enteritis and dogs treated with cyclosporine or glucocorticoids. 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 cystitis, pyeloneprhitis or other infectious complications has been reported in dogs or cats. A study of healthy female dogs identified bacteriuria in 8.9% of dogs and found no association with subsequent cystitis development over a 3 month follow-up period.[20]

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.[21] 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. Treatment is specifically not recommended for pre-menopausal, non-pregnant women, those with diabetes, older individuals in the community, elderly institutionalized individuals or individuals with spinal cord injuries. 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. A systematic review in humans concluded that while bacteriuria may be eliminated in the short-term, the effect is not sustained and re-colonization is common, leading to no impact on overall morbidity or mortality.[22] Further, two studies have reported significantly higher bacteriuria recurrence rates in women treated for asymptomatic bacteriuria compared to untreated controls.[23,24] Treated women also had higher rates of antimicrobial resistance.

There are few indications for culture of urine from animals without evidence of lower urinary tract disease. Culture of urine from animals with no evidence of urinary tract disease should not be performed when there would be no indication to treat based on a positive culture result. This includes patients with comordibities, particularly those with disease such as hyperadrenocorticism and diabetes mellitus, where subclinical bacteriuria is not uncommon.[25,26]

Bacterial concentration cannot differentiate subclinical bacteriuria from bacterial cystitis. SB is differentiated from bacterial cystitis by the absence of clinical signs and not by the bacterial load. Heavy growth on quantitative culture data (e.g. >100 000 CFU/ml) can be present in animals with subclinical bacteriuria[25] and there is no evidence that high CFU counts indicate a greater risk of disease development.

Treatment of subclinical bacteriuria is rarely indicated and is discouraged. In animals where it is unclear whether clinical signs are attributable to cystitis, a short course (e.g. 5 days) of antimicrobials as recommended for sporadic urinary tract infections could be considered. If there is no clinical response, antimicrobials should be discontinued, as an infectious process is unlikely.

Treatment of animals with pyuria or other cytological abnormalities but no clinical signs of lower urinary tract disease is not recommended. Previous guidelines[11] supported treatment of animals with no clinical signs but cytological evidence of inflammation (pyuria). However, treatment of pyuria in humans in the absence of clinical evidence of UTI is not recommended.[21] There is currently no evidence in veterinary medicine that would indicate a different approach to that taken in humans.

Treatment of subclinical bacteriuria caused by plaque-forming (*Corynebacterium urealyticum*) and urease producing (*e.g.* staphylococci) could be considered because of their associations with encrusting cystitis and struvite urolith formation, respectively.[27-30] Because of the potential difficulties in treating these conditions, consideration of a single short course of treatment, as described for sporadic cystitis, could be considered after confirming that bladder wall plaque or uroliths are not present. However, it is unknown whether this is a necessary or effective approach.

Upper Urinary Tract Infections (Pyelonephritis)

Given the potential severity, accurate and prompt diagnosis is required to institute effective treatment as soon as possible. Whenever pyelonephritis is suspected, culture and susceptibility testing should always be performed. As with cystitis, cystocentesis samples should be used for culture whenever possible. Parallel blood culture may also be useful. Imaging is particularly important to determine whether pyelonephritis may be present. Interpretation of susceptibility data should be based on antimicrobial breakpoints for serum rather than urine concentrations, since renal tissue levels are the key, not urine levels.

Immediate treatment is indicated, using an antimicrobial with good activity against Gram negative Enterobacteriaceae. If ascending infection is suspected, urine culture results obtained for diagnosis of cystitis might be the basis of initial therapy. If the upper UTI results from hematogenous spread, initial therapy should be based on cultures of blood or the infected site, whenever available. Otherwise, empirical therapy with a drug typically effective against Gram negatives should be chosen. Fluoroquinolones are the main recommendation based on their spectrum and efficacy for tissue-associated infections. Knowing resistance trends in urinary *E. coli* isolates in the practice can be helpful to guide initial therapy. Combination therapy can be considered initially, with changes potentially made based on culture results. If combination therapy was initiated and the isolate is susceptible to both drugs, one might be discontinued if supported by evidence of clinical response. If resistance is reported to one of the drugs, that antimicrobial should be discontinued. A second drug to which the isolate is susceptible should be substituted if the patient has not responded sufficiently; substitution is not necessary if patient response has been sufficient. There is little evidence to guide duration of treatment. Treatment of 4-6 weeks is often recommended and that is reasonable, although a shorter duration of therapy might be effective. Treatment of 4-6 weeks has previously been recommended for veterinary patients.[11] However, the recommended duration of therapy for acute bacterial pyelonephritis in children is 7-14 days. [31] For adult humans, 10-14 days for beta-lactams or trimethoprim-sulfamethoxazole and 7 days for ciprofloxacin are recommended.[32] There is no reason to suspect that a longer duration would be necessary for dogs and cats. In the absence of veterinary-specific data, the 10 to 14 days of treatment has now been recommended.

Table 1: Selected antimicrobial treatment options for urinary tract infections in the dog and cat (draft revision of [11]).

Drug	Dose	Comments
Amoxicillin	11-15 mg/kg PO q8-12h	Good first-line option for sporadic bacterial cystitis. Excreted in urine predominantly in active form if normal kidney function is present. *Klebsiella* spp. are resistant
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 (eg, low pH) can affect aminoglycoside activity, which should be considered.
Amoxicillin / clavulante	12.5-25 mg/kg POq12h (dose	Not established whether there is any advantage over amoxicillin alone for sporadic bacterial cystitis. Reasonable empiric chose

	based on combination of amoxicillin + clavulanate	when regional susceptibility data support a high prevalence of resistance to amoxicillin but susceptibility to amoxicillin-clavulanate.
Ampicillin		Not recommended because of poor oral bioavailability. Amoxicillin is preferred
Cephalexin, cefadroxil,	12-25 mg/q12h;	Enterococci are resistant. Narrow-spectrum activity; not active against Enterobacteriaceae when using the current breakpoint of 2 mcg/mL. In human medicine, higher breakpoints of 16 mcg/mL are used to predict activity for uncomplicated infections.
Cefovecin	8 mg/kg single SC injection. Can be repeated once after 7-14 days.	Duration and spectrum and longer than is typically needed, so not recommended for routine use. Should only be used in situations where oral treatment is problematic. Enterococci are resistant. Pharmacokinetic data are available to support the use in dogs and cats, with a duration of 14 days (dogs) and 21 days (cats).
Cefpodoxime proxetil	Dogs: 5 to 10 mg/kg q24h PO	More active than cephalexin or cefadroxil against Enterobacteriaceae when using the breakpoint of 2 mcg/mL for interpretation. Enterococci are resistant
Ceftiofur	Dogs: 2 mg/kg q12-24h SC	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 multidrug resistant infections with few other options. Myelosuppression can occur, particularly with long-term (e.g. >28d) therapy. Avoid contact by humans because of rare idiosyncratic aplastic anemia.
Ciprofloxacin	30 mg/kg PO q24h	Sometimes used because of lower cost than enrofloxacin. Lower and more variable oral bioavailability than approved veterinary fluoroquinolones. Difficult to justify over approved fluoroquinolones.
Doxycycline	5 mg/kg PO q12h	Not excreted in urine at high levels but can achieve levels that are effective against most pathogens. Reserved for infections caused by pathogens that are resistant to drugs that are actively excreted in urine in active form.
Enrofloxacin	5 mg/kg PO q24h (cats) 5-20 mg/kg q24h (dogs)	Some activity is attributed to conversion to ciprofloxacin. Reserve for documented resistant UTIs but good first line choice for pyelonephritis in dogs at the higher end of the dosing range. Considered first-line choice for prostatitis. Associated with risk of retinopathy in cats. Do not exceed 5 mg/kg/d of enrofloxacin in cats.
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*.
Marbofloxacin	2.7-5.5 mg/kg PO q24h	Reserve for documented resistant UTIs but good first line choice for pyelonephritis. Considered first-line choice for prostatitis. 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 pharmacologist prior to use.
Nitrofurantoin	4.4-5 mg/kg PO q8	Second line option for sporadic bacterial cystitis particularly when multidrug resistant pathogens are involved. Must not be used for pyelonephritis or other infections where tissue (vs urine) drug levels are needed
Orbifloxacin	Tablets: 2.5-7.5 mg/kg PO q24h Suspension (cats): 7.5 mg/kg q24h	Excreted in urine predominantly in active form. Reserve for documented resistant UTIs but good first line choice for pyelonephritis. Considered first-line choice for infections that involve the prostate. Not recommended for enterococci.
Trimethoprim-sulfa	15-30 mg/kg PO q12h Note: dosing is based on total trimethoprim + sulfadiazine concentration	Good first-line option. 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 re-evaluation 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.
Fosfomycin	40 mg/kg PO (with food) q12h	Should be reserved for multidrug resistant infections. Do not use in cats
Pradofloxacin	Dogs: 3-5 mg/kg PO once daily. Cats: 3-5 mg/kg q24h (tablets) or 5-7.5 mg/kg q24h (suspension)	Approved for dogs and cats in Europe and Canada. Approved only for cats in the U.S. (liquid suspension). Published evidence for efficacy treating bacterial cystitis in dogs and cats. Greater activity against some bacteria than older fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin). Theoretically a good first line choice for pyelonephritis, especially in cats.
Minocycline	Cats: 8.8 mg/kg q24h PO, (or 50 mg per cat). Dogs: 5 mg/kg q12h, PO.	Can be considered an alternative to doxycycline when a tetracycline is indicated but doxycycline is not available. However, urine drug levels are low and minocycline should be avoided when doxycycline is an option. Higher doses of 10 mg/kg can be used in dogs but is more likely to cause vomiting.
Florfenicol	Dogs:20 mg/kg IM q8h Cats: 22 mg/kg PO,IM q12h	Reserved for multidrug resistant infections with few other options. Sometimes used as an alternative to chloramphenicol to avoid haematopoietic adverse effects

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Antibiotic treatment of respiratory tract infections

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Introduction

Respiratory tract infections are not uncommon in dogs and cats, but can be difficult to manage for many reasons. A variety of different pathogens, including viruses and bacteria can be involved, sometimes in co-infections. The upper respiratory tract harbours a diverse bacterial microbiota and many (or most) potential causes of respiratory disease can be found in some healthy individuals. Definitive diagnosis of the presence of a bacterial infection can be difficult. Treatment options have not been well studied, including drug choices and duration of treatment. These factors mean that determining when and how to treat may be a challenge. There is also a wide spectrum of disease that may require markedly different approaches. Examples are provided below, along with a table of antimicrobial options (Table 1).

Feline upper respiratory tract disease (URTD)

This multifactorial syndrome can be caused by a range of bacterial and viral pathogens, and typically causes ocular and nasal discharge, epistaxis, sneezing and conjunctivitis. Disease may be acute or chronic, with chronic disease being a potential frustrating problem to manage.

Most cats with URTD have viral infections (FHV-1, calicivirus), but secondary bacterial infections can develop, particularly with staphylococci, streptococci, *E. coli* and *Pasteurella*. *Chlamydia felis*, *Bordetella bronchiseptica* and *Mycoplasma* may also be involved. Diagnosis is not often attempted because of the potential difficulty identifying the underlying cause and the limited impact a diagnosis has on treatment decisions.

Treatment recommendations

For acute disease, monitoring without antibiotics is recommended in most cases, particularly those that are acute and not severe. A 10 day observation period is reasonable if the cat has no evidence of fever, lethargy or anorexia accompanying the signs of URTD, signs that might indicate the progression to bacterial pneumonia.

When treatment is required, doxycycline is recommended for 7-10d as the first line choice. Amoxicillin would be an acceptable choice if *C. felis* and *Mycoplasma* are not highly suspected.

If there is poor response to antimicrobials, further diagnostic testing is indicated, not simply selection of a new drug.

For chronic disease, diagnostic testing is required to identify underlying causes that might need to be addressed. First line options for acute disease still apply. Use of drugs such as 3rd generation cephalosporins, fluoroquinolones or azithromycin should be reserved for situations where first line options are not viable.

If disease is recurrent, underlying problems cannot be identified or addressed, and there is a history of response to treatment, use of the same drug to which there was a positive response the last time is reasonable.

Canine upper respiratory disease complex (CIDRC)

This common problem (often referred to as kennel cough) can be caused by many different viruses and bacteria. It is highly contagious and usually minimally virulent, and is most often self-limiting. Testing is not often performed because of limited impact on treatment in acute, sporadic cases. Therefore, empirical treatment options are usually required.

Treatment recommendations

Observation for 10 days without antibiotics is recommended as disease will usual resolve without antimicrobials. Antimicrobials should be recommended in dogs with fever, lethargy or inappetance plus mucopurulent nasal discharge. If there is no evidence of bacterial pneumonia, doxycycline for 7-10 days is recommended. Amoxicillin or amoxicillin/clavulanic acid are considerations is treatment with doxycycline fails or is not possible (e.g. not well tolerated), but there is some resistance of *Bordetella* to these drugs and they are ineffective against *Mycoplasma.*

Pneumonia

Various bacteria may be involved, with *B. bronchiseptica*, *Mycoplasma* spp., *Streptococcus equi zooepidemicus and Streptococcus canis* being potential primary pathogens and *Escherichia coli*, *Pasteurella* spp., *Streptococcus* spp, *B. bronchiseptica*, *Enterococcus* spp., *Mycoplasma* spp., *S. pseudintermedius* and other coagulase-positive *Staphylococcus* spp., and *Pseudomonas* spp.. being opportunistic agents. Treatment is ideally based on culture of lower airway specimens, but empirical treatment is needed while awaiting culture results

Treatment recommendations

If infection is suspected to have been caused by *Bordetella* or *Mycoplasma* and there is no evidence of systemic disease (fever, dehydration, lethargy, respiratory distress), doxycycline is recommended.

If aspiration pneumonia is suspected, a parenteral beta-lactam (e.g. ampicillin, ampicillin/sulbactam, first generation cephalosporin such as cefazolin) may be adequate.

If evidence of sepsis is present, broader spectrum coverage, including good activity against gram negative bacteria, is indicated. This should consistent of a drug with good gram positive activity (e.g. ampicillin, ampicillin/sulbactam, first generation cephalosporin such as cefazolin) plus a fluoroquinolone. Treatment can be refined based on culture results, when they become available.

Table 1: Selected antimicrobials for the treatment of respiratory infections in dogs and cats. From The International Society of Companion Animal Infectious Diseases guidelines (Lappin et al, in press).

Drug	**Dose**	**Comments**
Amikacin	Dogs: 15 mg/kg, IV/IM/SC, q24h Cats: 10 mg/kg, IV/IM/SC, q24h	Not recommended for routine use but may be useful for treatment of multidrug resistant organisms or if parenteral enrofloxacin or ciprofloxacin are contraindicated. Potentially nephrotoxic. Avoid in dehydrated animals and those with renal insufficiency.
Amoxicillin	22 mg/kg, PO, q8-12h	May be useful for treatment of secondary bacterial URI caused by *Pasteurella* spp. and *Streptococcus* spp., some *Staphylococcus* spp. and many anaerobic bacteria. Ineffective against beta-lactamase producing bacteria, most *Bordetella bronchiseptica* isolates, all *Mycoplasma* spp., and *Chlamydia felis* in cats.
Amoxicillin-clavulanate	Dogs: 11 mg/kg, PO, q8-12h Cats: 12.5 mg/kg, PO, q12h	Used as a first-line option for secondary bacterial URI from *Pasteurella* spp., *Streptococcus* spp., methicillin-susceptible *Staphylococcus* spp. (including penicillase-producing strains), many anaerobic bacteria, and most *B. bronchiseptica* isolates. Ineffective against all *Mycoplasma* spp., and inferior to other drugs for *C. felis* in cats.
Ampicillin-sulbactam	20 mg/kg, IV, IM, q6-8h	Used alone parenterally for cases with uncomplicated secondary bacterial pneumonia (gram-positive and anaerobic bacteria). Used concurrently with another drug with wider gram-negative activity if life-threatening disease exists.
Ampicillin sodium	22-30 mg/kg, IV, SQ, q8h	Used parenterally for cases with uncomplicated secondary bacterial pneumonia (gram-positive and anaerobic bacteria). Used concurrently with another drug with gram-negative activity if life-threatening disease exists.
Azithromycin	5-10 mg/kg, PO, q12h day 1 and then q3 days (Longer intervals are not indicated)	Used for primary bacterial diseases (in particular *Mycoplasma* spp.) and for pneumonia of undetermined etiology because the spectrum includes *Toxoplasma gondii* and *Neospora caninum*.
Cefazolin	25 mg/kg, SQ, IM, IV, q6h	Used parenterally for cases with uncomplicated secondary bacterial pneumonia (gram-positive and anaerobic bacteria). Used concurrently with another drug with wider gram-negative activity if life-threatening disease exists. Ineffective against *B. bronchiseptica*, *Mycoplasma* spp., and *C. felis* in cats, and enterococci.
Cefovecin	8 mg/kg, SC, once. Can be repeated once after 7-14 days.	May be effective for treatment of secondary bacterial URI caused by *Pasteurella* spp., some *Staphylococcus pseudintermedius* and *Streptococcus* spp.. Ineffective for *B. bronchiseptica*, *Mycoplasma* spp., and *C. felis* in cats and *Enterococcus* spp.. Pharmacokinetic data are available to support the use in dogs and cats, with a duration of 14 days (dogs) and 21 days (cats).
Chloramphenicol	Dogs: 50 mg/kg, PO, q8h Cats: 50 mg/cat, PO q12h	Reserved for multidrug resistant infections with few other options. Effective for the primary bacterial pathogens, penetrates tissues well, and has an excellent spectrum against anaerobes and so may be considered for treatment of pneumonia when the owner cannot afford dual antimicrobial agent therapy. Myelosuppression can occur, particularly with long term therapy. Owners should be instructed to wear gloves when handling the drug because of rare idiosyncratic aplastic anemia in humans.

Clindamycin	Dogs: 10 mg/kg, PO, SC, q12h Cats: 10-15 mg/kg, PO, SC, q12h	Activity against most anaerobic bacteria, many gram-positive bacteria and some mycoplasmas. Not effective for most gram-negative bacteria and some *Bacterioides* spp..
Doxycycline	5 mg/kg, PO, q12h Or 10 mg/kg, PO, q24h	Used for dogs or cats with URI, CIRDC, or bronchitis that is likely to be associated with *B. bronchiseptica*, *Mycoplasma* spp., and *C. felis* (cats). An injectable formulation is available if parenteral administration is needed. Either the hyclate or monohydrate salts can be used. Can be used in kittens and puppies > 4 weeks of age without teeth browning.
Fluoroquinolones	Various	Active against most isolates of *B. bronchiseptica*, *Mycoplasma* spp., and *C. felis* (cats) as well as many secondary gram-negative and gram-positive bacteria. Practically no activity against *Enterococcus* spp and anaerobic bacteria. Doses higher than 5 mg/kg/d of enrofloxacin in cats are not recommended because of retinopathy, while doses of 5 mg/kg or lower are likely associated with increased resistance potential, so this drug is best avoided in cats. All quinolones are associated with cartilage problems in growing puppies and kittens. Enrofloxacin is not approved for parenteral use in cats and is not soluble enough to be injected directly. It can precipitate and can chelate with cations in some fluid solutions.
Gentamicin	Dogs: 9-14 mg/kg, IV, q24h Cats: 5-8 mg/kg, IV, q24h	Not recommended for routine use but may be useful for treatment of multidrug resistant organisms or if parenteral enrofloxacin is contraindicated. Potentially nephrotoxic. Avoid in dehydrated animals and those with renal insufficiency.
Imipenem-cilastatin	3-10 mg/kg, IV, IM q8h	Reserve for treatment of multidrug resistant infections, particularly those caused by *Enterobacteriaceae* or *Pseudomonas aeruginosa*. Recommend consultation with a respiratory or infectious disease veterinary specialist or veterinary pharmacologist prior to use.
Marbofloxacin	2.7-5.5 mg/kg PO q24h	Effective for the primary bacterial pathogens *B. bronchiseptica*, *Mycoplasma* spp., and *C. felis* (cats) as well as many secondary infections with gram-negative and gram-positive organisms. Limited efficacy against *Enterococcus* spp. and anaerobic bacteria. Available as an injectable solution in some countries.
Meropenem	Dogs: 8.5 mg/kg SC 12h Or 24 mg/kg IV q12h Cats: 10 mg/kg q12h, SC, IM, IV	Reserve for treatment of multidrug resistant infections, particularly those caused by *Enterobacteriaceae* or *Pseudomonas aeruginosa*. Recommend consultation with an infectious disease veterinary specialist or veterinary pharmacologist prior to use.
Minocycline	Dogs: 5 mg/kg, PO, q12h Cats: 8.8 mg/kg PO q24h or 50 mg/patient PO q24h	Similar to doxycycline and can be used for dogs or cats with URI, CIRDC, or bronchitis that is likely to be associated with *B. bronchiseptica*, *Mycoplasma* spp., and *C. felis* (cats).
Trimethoprim-sulfamethoxazole or trimethoprim-sulfadiazine	15 mg/kg PO q12h Note: dosing is based on total trimethoprim + sulfadiazine concentration	Generally avoided in respiratory tract infections that may involve anaerobic bacteria (particularly pyothorax). Ineffective for primary bacterial pathogens other than *Streptococcus* spp. Concerns regarding adverse effects in some dogs, especially with prolonged therapy. If prolonged (>7 d) therapy is anticipated, baseline Schirmer's tear testing is recommended, with periodic re-evaluation 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.

Patient-Centric Antibiotic Stewardship

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INTRODUCTION

Antimicrobials revolutionized human and veterinary medicine; however, the parallel emergence and dissemination of antimicrobial resistance continues to compromise these gains. Antimicrobial resistance (AMR) has been called the global health crisis of our time. Effective antimicrobials are required for the health and safety humans and animals, and AMR puts modern healthcare at risk, with challenges ranging from complications treating common and simple conditions such as urinary tract infections or resistance that threatens the use of complex conditions such as cancer care and surgery. Antimicrobials are also important for the health and welfare of food producing animals, facilitating humane, safe and economically viable food production and helping assure food security. The dire economic consequences of AMR cannot be overstated. The World Bank estimates that, by 2050, AMR will result in global economic damage at least equivalent to the financial collapse of 2008 if left unchallenged, and no country will be spared.

WHAT IS ANTIMICROBIAL STEWARDSHIP?

Antimicrobial stewardship is a coordinated approach to optimizing the use of antimicrobials, maximizing patient care and while minimizing the risk of resistance, toxicity or other adverse events. This involves a multifaceted approach to determine **when** to prescribe antimicrobials, **what** drug, dose and duration, **how** they are administered and **whether** other approaches are needed in addition to or in lieu of antimicrobials (e.g. surgery, wound care, management of underlying disease).

While the concept of antimicrobial stewardship is now attracting much attention, there is sometimes the perception that an antimicrobial stewardship program (ASP) is meant to be restrictive and will therefore negatively impact the practice of veterinary medicine. While some aspects of an ASP may implement controls, an ASP is not meant to complicate patient care, remove access to needed antimicrobials or decrease practice efficiency. Rather, a well structured and functioning ASP can improve patient care and facilitate timely and effective treatment.

Despite the increasing attention being patient towards antimicrobial stewardship, there has been limited specific implementation of ASPs in veterinary clinics and limited practice- or patient-level guidance. While general statements about the need for 'prudent' use of antimicrobials have existed in veterinary medicine for some time,[1-4] practical clinical guidance has been limited. However, in recent years, there has been an increase in available information, including broad national treatment guidelines, as well as detailed guidelines for specific diseases (e.g. urinary tract infections in dogs and cats).[5]

In human medicine, the field of antimicrobial stewardship has evolved into comprehensive program run by people specializing in the field, using a multifaceted approach to address a range of issues related to antimicrobial use. While some aspects of human stewardship programs do not apply to veterinary medicine, or are most relevant for large referral facilities, a large percentage of the core human strategies can be effectively and practically implemented in veterinary medicine. The state of antimicrobial stewardship in veterinary medicine is perhaps similar to the situation in community medicine in humans, an area where stewardship activities have lagged far behind hospitals. Many of the issues faced by community healthcare are similar to those faced by veterinary practices, and as the ASP field advances in human community care, there should be increasing potential for cross-application of new ideas and approaches. Regardless, there are initiatives that virtually any veterinary clinic can undertake now. Further, as there is increased scrutiny on antimicrobial resistance and antimicrobial use in veterinary medicine, development and implementation of practical ASPs will be necessary to optimize patient care and as a method of due diligence, to help ensure that veterinarians have access to antimicrobials.

COMPONENTS OF ANTIMICROBIAL STEWARDSHIP

Antimicrobial stewardship is a multi-modal approach to the practice of medicine that goes beyond specific aspects of antimicrobial use. An ASP obviously has a major emphasis on specific aspects of drug prescription and use. However, a strong ASP has broader aspects to reduce the need for antimicrobials through preventing disease and promptly identifying patients that require antimicrobials and those that do not. It also fosters been communication and education of all players in the prescribing cascade (attending clinician, diagnostic laboratory, pharmacy, owner) to facilitate optimal use and remove pressures to use antimicrobials in situations where they are not indicated.

Virtually all clinicians practice some form of antimicrobial stewardship on a daily basis, through decisions about when and how to use antimicrobials, and through measures taken the reduce the risk of disease. Therefore, implementation of an ASP should not be approached as a paradigm shift, but rather an evolution of core principles of medicine. There is a wide range of potential components of an antimicrobial stewardship program (Table 1). The feasibility and potential benefits of these vary, with some representing rather easy-to-implement and potentially high yield measures, and others that can be categorized as useful to more complex and lower priority.

Table 1: Potential components of a veterinary antimicrobial stewardship program

Antibiogram data collection and use	Automatic stop orders
Cascading microbiology susceptibility reporting	Checklists (e.g. surgical)
Computerized decision support systems	De-escalation and streaming
Disease-specific treatment guidelines	Surgical prophylaxis guidelines
Dose optimization	Formulary restriction
Formulary restriction with pre-authorization	Formulary restriction with authorization
Computer-based identification of inappropriate pathogen/drug combinations	Improved antimicrobial documentation
Improved diagnostics	IV to oral conversion
Prescriber education	User (owner) education
Prevention of treatment of non-infectious conditions	Promotion of timely and appropriate microbiological sampling
Prospective audit with feedback (clinician/service/facility)	Scheduled antimicrobial re-assessments (antibiotic time-outs)
Strategic microbiology results reporting	Targeted review for redundant therapy/therapeutic duplication
Therapeutic drug monitoring	

IMPLEMENTATION OF AN ANTIMICROBIAL STEWARDSHIP PROGRAM

The approach to an ASP will vary greatly between facilities, based on a range of factors such as the nature of the caseload, the prevalence of resistant pathogens, the current state of antimicrobial use, access to specialists, access to a pharmacist, clinician motivation, management motivation and level of understanding of the issues. Yet, any practice can implement some components of an effective ASP with little effort, time, cost or access to other personnel. Often, starting with some easy measures (low hanging fruit) is useful to facilitate acceptance of change, with addition of new measures over time as people realize the potential benefits, have increased awareness and understand that an ASP is meant to help, not hamper, patient care.

RESOURCES

While clinical antimicrobial stewardship is still in its infancy in veterinary medicine, a variety of resources are available. These include general position statements,[4,6-8] disease-specific diagnosis and treatment guidelines,[5,9-12] human healthcare ASP resources and ASP program websites (Table 2). There are also national broad treatment guidelines, such as those from the Australian Infectious Disease Advisory Panel (http://www.ava.com.au/sites/default/files/AVA_website/pdfs/AIDAP%20prescribing%20guidelines.pdf) and Danish Small Animal Veterinary Association (http://www.fecava.org/sites/default/files/files/DSAVA_AntibioticGuidelines%20-%20v1-1_3(1).pdf). These can provide the foundation for a facility-specific ASP in any veterinary practice, although more specific and practical guidance for veterinary facilities will hopefully be increasingly available in the near future.

Table 2: Examples of antimicrobial stewardship program resources

Source	Access
Australian National Centre for Antimicrobial Stewardship	https://www.ncas-australia.org/
BSAVA	https://www.bsava.com/Resources/Veterinary-resources/PROTECT
Centers for Disease Control and Prevention	https://www.cdc.gov/antibiotic-use/healthcare/implementation/core-elements.html
European Centre for Disease Control	https://ecdc.europa.eu/en/publications-data/directory-guidance-prevention-and-control/antimicrobial-stewardship
Infectious Diseases Society of America	http://www.idsociety.org/Stewardship_Policy/
Public Health Ontario	https://www.publichealthontario.ca/en/BrowseByTopic/InfectiousDiseases/AntimicrobialStewardshipProgram/Pages/Antimicrobial-Stewardship-Program.aspx
Society for Healthcare Epidemiology of America	https://www.shea-online.org/index.php/practice-resources/priority-topics/antimicrobial-stewardship

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