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International Society for Companion Animal Infectious Diseases (ISCAID) guidelines for the diagnosis and management of bacterial urinary tract infections in dogs and cats

J. Scott Weese[a,*], Joseph Blondeau[b,c], Dawn Boothe[d], Luca G. Guardabassi[e,f], Nigel Gumley[g], Mark Papich[h], Lisbeth Rem Jessen[i], Michael Lappin[j], Shelley Rankin[k], Jodi L. Westropp[l], Jane Sykes[l]

[a] Dept of Pathobiology, Ontario Veterinary College, University of Guelph, Guelph, ON, N1G2W1, Canada
[b] Clinical Microbiology, Royal University Hospital and the Saskatchewan Health Authority, Saskatoon, SK, Canada
[c] Departments of Microbiology and Immunology, Pathology and Laboratory Medicine and Ophthalmology, University of Saskatchewan, Saskatoon, SK, Canada
[d] Department of Anatomy, Physiology and Pharmacology, Auburn University, 36849, USA
[e] Department of Veterinary and Animal Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Stigbøjlen 4, 1870 Frederiksberg C, Denmark
[f] Department of Pathobiology and Population Sciences, The Royal Veterinary College, Hawkshead Lane, North Mymms, Hatfield, Herts, AL9 7TA, United Kingdom
[g] Cedarview Animal Hospital, 4100 Strandherd Dr, #106, Ottawa, ON K2J 0V2, Canada
[h] Department of Molecular Biomedical Sciences, North Carolina State University, College of Veterinary Medicine,4700 Hillsborough Street, Raleigh, NC 27606, USA
[i] Veterinary Clinical Sciences, Faculty of Health and Medical Sciences, University of Copenhagen, Dyrlaegevej 16, 1870 Frederiksberg C, Denmark
[j] Department of Clinical Sciences, Colorado State University, 300 West Drake Road, Fort Collins, CO 80523, USA
[k] School of Veterinary Medicine, University of Pennsylvania, 3800 Spruce St, Philadelphia, PA 19104, USA
[l] School of Veterinary Medicine, Department of Medicine & Epidemiology, 2108 Tupper Hall, University of California-Davis, Davis, CA 95616, USA

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ABSTRACT

Urinary tract disease is a common clinical presentation in dogs and cats, and a common reason for antimicrobial prescription. This document is a revision and expansion on the 2011 Antimicrobial Use Guidelines for Treatment of Urinary Tract Disease in Dogs and Cats, providing recommendations for diagnosis and management of sporadic bacterial cystitis, recurrent bacterial cystitis, pyelonephritis, bacterial prostatitis, and subclinical bacteriuria. Issues pertaining to urinary catheters, medical dissolution of uroliths and prophylaxis for urological procedures are also addressed.

Introduction

Bacterial urinary tract disease is a common cause of morbidity in dogs and cats, and among the leading reasons for antimicrobial use. Improper therapy can lead to a variety of health concerns for the dog or cat (e.g. failure to resolve infection, development of antimicrobial resistance), economic (e.g. need for repeated or prolonged treatment), public health (e.g. antimicrobial resistance) and regulatory (e.g. antimicrobial use) concerns. In human medicine, antimicrobial use guidelines such as those developed by the Infectious Diseases Society of America (IDSA) provide guidance to physicians on management of various infectious diseases, including urinary tract infection (UTIs) (Nicolle et al., 2005; Warren et al., 1999). Such guidelines can be directly used or can form the basis of hospital-level antimicrobial use guidelines. The impact of national or international guidelines is difficult to assess, but implementation of antimicrobial use guidelines at the hospital level has been shown to significantly improve antimicrobial prescribing practices, either alone or as part of a broader antimicrobial stewardship program (Deuster et al., 2010; Metjian et al., 2008; Toth et al., 2010).

This document is a revision of one previously published from the Antimicrobial Guidelines Working Group of the International Society for Companion Animal Infectious Diseases (ISCAID) (Weese et al., 2011). These guidelines expand on the previous guideline and provide some different recommendations based on advances in the field since the initial version was published. There is still a paucity of objective data, particularly high-level data such as randomized

* Corresponding author.
E-mail address: jsweese@uoguelph.ca (J. S. Weese).

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controlled trials to guide antimicrobial treatment recommendations. As with the previous guidelines and those pertaining to other diseases (Hillier et al., 2014; Lappin et al., 2017), recommendations are based on available data from veterinary and human medicine, along with expert opinion, considering principles of infectious diseases, antimicrobial therapy, antimicrobial resistance, pharmacology and internal medicine.

Specific recommendations were reached through an iterative process. Following this internal process, draft guidelines were submitted to a panel of six experts for further comments, and final discussion and approval. Any dissenting views led to further discussion by the Working Group.

As with all guidelines, these should be interpreted as general recommendations and not mandates, that are consistent with good clinical practice and appropriate for the majority of cases but which cannot encompass the wide range of situations that are encountered in clinical practice. Case by case decisions still need to be made by the attending clinician. These guidelines should not be considered standards of care that must be followed in all circumstances. Rather, they should be considered the basis of decision-making, realizing that different or additional approaches may be indicated in some cases. Additionally, regional differences (e.g. antimicrobial resistance rates, antimicrobial availability, prescribing regulations) exist and those must be considered. The Working Group realizes that this is an international document and not all antimicrobial agents discussed are available, approved or allowed, in every country.

Sporadic bacterial cystitis

Sporadic bacterial cystitis is a common condition in dogs, and occasionally encountered in cats, in which a bacterial infection of the bladder results in inflammation and corresponding clinical signs, which can include pollakiuria, dysuria, stranguria, hematuria, or a combination of these signs. It is a common reason for veterinary visits and antimicrobial administration to both dogs and cats (Murphy et al., 2012; Rantala et al., 2004). Previously, 'simple uncomplicated' or 'complicated' urinary tract infection (UTI) has been used to describe bacterial cystitis in dogs and cats (Weese et al., 2011); however, clear understanding of what those categories mean is lacking. Further, as opposed to humans where uncomplicated UTI are commonly identified in some populations (particularly young, healthy, sexually active women), it is unclear whether 'uncomplicated' disease truly occurs in dogs, or whether there is an underlying risk factor in most cases. Despite the importance of this condition, high-level data on antimicrobial treatment are lacking (Jessen et al., 2015).

In cats, bacterial cystitis has often been defined as a 'complicated' UTI due to the frequent presence of comorbidities and the increased incidence in older cats. However, the presence of comorbidities does not *per se* imply a more complicated infection, and there is no evidence to suggest that sporadically occurring bacterial cystitis is more 'complicated' to manage in cats than in dogs. The most important consideration when approaching a feline with evidence of lower urinary tract signs (LUTS) is realization that the majority of cats (particularly young cats) with LUTS do not have bacterial cystitis (Buffington et al., 1997; Lekcharoensuk et al., 2001; Sævik et al., 2011); feline idiopathic cystitis or urolithiasis is much more common in this population. Special attention is warranted to confirm the diagnosis and avoid overtreatment with antimicrobials in individuals with non-bacterial conditions such as feline idiopathic/interstitial cystitis (FIC).

In humans, there has been extensive study of treatment regimens, including comparison of different antimicrobials and treatment durations. Veterinary data are limited and recommendations for drugs and duration have previously been made predominantly based on personal observations and opinions. The previous version of these guidelines recommended a 7–10 day duration of antimicrobial administration. It included a caveat that the shorter duration of therapy administered in humans might be effective, but that data are lacking. In the interim, canine studies have provided some support for the effectiveness of shorter duration therapy (Table 2). Further study is needed to more specifically compare different dosing regimens and different antimicrobials, but these studies indicate that shorter durations, as are used in humans, may be effective.

Classification

1) Sporadic bacterial cystitis (sometimes referred to as 'simple uncomplicated UTI') is a sporadic bacterial infection of the urinary bladder with compatible lower urinary tract signs in dogs or cats. From here on this will be referred to as sporadic cystitis.
2) Sporadic cystitis been previously used to describe animals that, (a) are otherwise healthy non-pregnant females or neutered males; (b) have no known urinary tract anatomical and functional abnormalities or relevant comorbidities (e.g. endocrinopathy, intervertebral disk disease); and, (c) have had fewer than three episodes of known or suspected episodes of bacterial cystitis in the preceding 12 months. However, animals 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 12 months) sporadic cystitis in individuals with urinary tract abnormalities or comorbidities should be approached as is described here.
3) Sporadic cystitis appears to be rare in intact male dogs and bacterial prostatitis must be considered in intact male dogs with lower urinary tract signs.
4) Animals that have experienced three or more episodes of clinical cystitis within the preceding 12 months should be managed as described in the 'Recurrent bacterial cystitis' section of this document. Animals with bacteriuria in the absence of clinical signs should be managed as described for 'Subclinical bacteriuria' section of this document. A single recurrence of sporadic cystitis within the preceding 3 months should be approached as described for 'Recurrent bacterial cystitis'.

Diagnosis

1) Diagnosis is based on the presence of lower urinary tract signs, ideally with concurrent evidence supporting bacterial cystitis (e.g. hematuria, pyuria, cytologically evident bacteriuria) and bacterial culture results.
2) Urinalysis (dipstick, urine specific gravity and cytological examination of the sediment) should be performed in all cases to providing supporting evidence and detect potential comorbidities (e.g. glucosuria, crystalluria).
3) Aerobic bacterial urine culture is preferred for all cases of suspected bacterial cystitis but empirical therapy in lieu of culture can be justified in dogs with suspected sporadic cystitis, particularly in animals with limited previous antimicrobial exposure and in situations where the likely pathogens and susceptibility patterns are predictable. In cats, diagnosis of bacterial cystitis should be confirmed by aerobic bacterial urine culture in all cases due to the low likelihood of bacterial cystitis in cats with LUTS.
4) Specimens for culture should be collected by cystocentesis unless there is a contraindication (which would rarely be

present in animals with sporadic cystitis) or significant difficulties in sample collection are anticipated (e.g. from a large, morbidly obese dog). Ultrasound guidance facilitates collection sample by cystocentesis and also provides an opportunity to assess the bladder for abnormalities such as uroliths, or masses. If samples cannot be processed immediately, they should be refrigerated and processed for culture within 24 h of collection (Patterson et al., 2016).

5) Culture of voided samples should only be performed when cystocentesis is contraindicated 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 or cultured in-house (Sørensen et al., 2016). The level of growth (≥100,000 colony forming units (CFU)/mL), bacterial species (i.e. isolation of common uropathogens such as Enterobacteriaceae or coagulase-positive staphylococci) and whether pure growth is present are important factors to assess when evaluating culture results from voided samples, along with urine cytology and clinical signs. Laboratories should be informed whether urine samples are cystocentesis or voided samples, to ensure that quantitative culture is performed on voided samples.
6) There has been inadequate study of samples collected via newly placed urinary catheters; however, criteria for voided samples might be similarly applied.
7) Potential comorbidities (Table 1) should be considered, particularly in young and old animals. While extensive diagnostic testing may not be indicated in response to a single episode of sporadic cystitis, consideration of why an infection occurred is important.

Treatment

1) 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 (Bleidorn et al., 2016; Gágyor et al., 2015), which could be applied to sporadic cystitis in cats and dogs. Consideration can be given to prescribing an initial course of analgesics (e.g. NSAIDs) and adding antimicrobials 3–4 days later if clinical signs persist or worsen. Regardless, NSAIDs (use with caution in cats) should be *considered* during the initial treatment period to help ameliorate clinical signs. To avoid unnecessary antimicrobial use in cats, withholding antimicrobial treatment pending the result of aerobic urine culture is reasonable.
2) Optimal empirical choices vary based on the pathogen and resistance patterns in the region. However, amoxicillin (Table 3) 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-sulfonamides (trimethoprim-sulfadiazine, trimethoprim-sulfamethoxazole) are other first tier options but may be associated with greater adverse effects. However, the likelihood of adverse effects is low with short courses of therapy as are recommended below.
3) The recommended duration of therapy is 3–5 days. The short end of that dosing period may be optimal, but veterinary research to support this is currently limited.
4) Nitrofurantoin, fluoroquinolones and 3rd generation cephalosporins should be reserved for sporadic cystitis where amoxicillin (±clavulanic acid) and trimethoprim-sulfonamide are not appropriate based on culture and susceptibility testing results or patient factors. These drugs can be effective but uncommonly needed, and their use in animals is scrutinized because of concerns regarding antimicrobial resistance and public health. Rarely, the dosing regimens that some of these drugs offer (e.g. once daily administration or single injection) may be required for proper treatment, and owner compliance is an important consideration. However, clinicians must differentiate between need and convenience when choosing one of these drugs over recommended first line options. Additionally, the US FDA has discouraged routine use of fluoroquinolones in humans for uncomplicated infections because of adverse effects (e.g. joint, tendon and nerve damage) (US Food and Drug Association, 2016). It is not necessary to administer fluoroquinolones in most cases of sporadic cystitis when other alternatives exist.
5) Treatment of intact male dogs with no evidence of prostatitis (see prostatitis section), as well as dogs with comorbidities not involving the urinary tract and with non-recurrent infections should be approached as described above, with the understanding the underlying factors might increase the likelihood of recurrence.
6) Clinicians should be aware of local (ideally clinic-level) antimicrobial susceptibility patterns to help guide empirical choices. If the expected incidence of treatment failure to a given antimicrobial increases, an alternate antimicrobial should be considered. However, care must be taken when interpreting potentially biased data, such as culture data obtained predominantly from specimens submitted from animals with refractory or recurrent cystitis. Clinics are encouraged to collect surveillance data on pathogen susceptibility patterns and clinical response to guide optimal empirical therapy. Consultations with their laboratory microbiologists are encouraged.
7) Infusion of substances (e.g. antimicrobials, anti-inflammatories, biocides) into the bladder via urinary catheter is not recommended because of a lack of evidence of efficacy and the potential for iatrogenic infection, trauma from catheterization or irritation of the bladder from infusates.
8) There is currently no evidence that adjunctive treatment measures (e.g. cranberry extract, D-mannose) are useful for treatment of sporadic cystitis.

Table 1
Comorbidities that should be considered in a dog or cat with bacterial cystitis.

Endocrinopathy
Kidney disease
Obesity
Abnormal vulvar conformation
Congenital abnormalities of the urogenital tract (e.g. ectopic ureter, mesonephric duct abnormalities)
Prostatic disease
Bladder tumor
Polypoid cystitis
Urolithiasis
Immunosuppressive therapy
Rectal fistula
Urinary incontinence/retention

Follow up

1) Lack of clinical response within 48 h of starting appropriate antimicrobials should prompt further investigation to determine whether cystitis is actually present and identify complicating factors.

Table 2
Clinical studies evaluating treatment duration for sporadic bacterial cystitis in dogs.

Study population	Treatments	Results	Reference
Female dogs (n = 38) with lower urinary tract signs	Trimethoprim sulfamethoxazole (15 mg/kg PO every 12 h for 3 days) vs. cephalexin (20 mg/kg PO every 12 h for 10 days)	No difference in clinical cure rates or microbiological cure 3, 4 or >30 days after treatment. Long-term microbiological cure rates were low in both groups	Clare et al. (2014)
Adult otherwise healthy dogs with clinical evidence of cystitis and cystocentesis culture yielding >1000 CFU/mL	Enrofloxacin (18–20 mg/kg PO every 24 h for 3 days) vs. amoxicillin/clavulanic acid (13.75–25 mg/kg PO every 12 h for 14 days)	Enrofloxacin was not inferior (microbiological or clinical cure rates) compared to amoxicillin/clavulanic acid	Westropp et al. (2012)

2) If initial culture results indicate resistance to the empirical antimicrobial that was chosen, the drug should be changed unless there has been good clinical response.
3) Empirically changing antimicrobials in response to poor initial response to treatment is not recommended. If clinical failure has been documented, the cause must be determined as it may be unlikely that a different drug will result in a better outcome. Animals with partial or complete clinical failure to treatment should be re-examined. Unless the initial culture results indicated resistance to the antimicrobial that was used empirically, or poor owner compliance is documented, prescribing a new course of antimicrobials in the absence of further investigation of the reason for clinical failure is not recommended.
4) Post-treatment urinalysis or urine culture is **not** recommended for sporadic cystitis when clinical signs have resolved.

Recurrent bacterial cystitis

In human medicine, recurrent bacterial cystitis implies a diagnosis of three or more episodes of clinical bacterial cystitis in the preceding 12 months or two or more episodes in the preceding 6 months (Arnold et al., 2016a, 2016b; Foxman, 1990). This definition has also been adopted in veterinary medicine. Recurrent bacterial cystitis (hereafter referred to as recurrent cystitis) may result from relapsing or persistent infection, or reinfection. Consideration of which of these is likely present can be useful for determining the diagnostic plan (e.g. evaluation of a nidus of infection vs. reasons for susceptibility to repeated infections).

Diagnosis

Since recurrent cystitis can be associated with an identifiable underlying cause (Table 1), identification and management of relevant risk factors and comorbidities is critical for long-term success. While identification of an underlying cause is not always possible, and while some identified problems cannot be effectively managed, repeated antimicrobial administration is unlikely to provide long-term cure and can be associated with antimicrobial resistance, treatment costs and risks of adverse effects from the antimicrobials.

Ultrasound, plain radiography, contrast imaging or possibly cystoscopy may be considered for refractory clinical recurrent cystitis cases to investigate further for underlying comorbidities and obtain a biopsy of the bladder mucosa, if clinically indicated. If clinical signs persist despite negative urine cultures, biopsies of bladder mucosa can be obtained during cystoscopy and submitted for culture and histological examination to evaluate for deep-seated bladder infections or other causes. When documented, selection of antimicrobials that achieve adequate concentrations in tissue (e.g. fluoroquinolones, cephalosporins, trimethoprim-sulfonamides) may be of benefit, but evidence for this statement is currently lacking. However, cystoscopy for recurrent bacterial cystitis in humans is not often recommended (Lawrentschuk et al., 2006).

1) Urine culture, ideally from a sample collected via cystocentesis, should be performed in all animals with recurrent cystitis.
2) Repeated prescribing of antimicrobials to patients that have not fully responded in the past, without exploration of underlying causes, should be avoided. A diagnostic plan should be established for every animal with recurrent cystitis.
3) If the pathogen isolated from the animal with recurrent infection is different from previous organisms isolated, reinfection is likely and efforts should be undertaken to identify and address any predisposing factors (see Table 1).
4) For relapsing, refractory and persistent infections, it is important to be certain the antimicrobial is achieving adequate concentrations in the bladder to clear the infection. A review of the antimicrobial, dose, dosing regimen, antimicrobial susceptibility pattern of the isolate and client compliance should be performed to determine whether an appropriate initial therapy was provided. If the drug, dosing regimen and compliance were adequate, efforts should be undertaken to identify and address any predisposing factors.

Treatment

Previous guidelines supported long durations (4 weeks) of antimicrobials for recurrent cystitis (Weese et al., 2011). However, recurrent cystitis encompasses a broad range of conditions, including repeated and relatively uncomplicated infections that likely respond quickly to antimicrobials and others with marked bladder pathology that complicates treatment. Broad recommendations for treatment duration are difficult because of this variation. In human medicine, several studies support short-course therapy for acute and recurrent bacterial cystitis (Arnold et al., 2016b). No evidence in dogs or cats exists to support or refute this statement for recurrent cystitis in veterinary medicine.

The goals of treatment must be considered. The primary objective is clinical cure with minimal risk of adverse effects (including antimicrobial resistance). Microbiological cure (elimination of the offending organism) is desirable but not necessarily achievable or required for short- or long-term clinical resolution.

1) Depending on the severity of clinical signs and owner's ability to observe the animal, treatment with analgesics (e.g. NSAIDs) alone could be considered while awaiting urine culture results. However, empirical therapy is reasonable and should be approached as is described for 'Sporadic bacterial cystitis'.
2) If empirical antimicrobials are initially prescribed, antimicrobial choice should be re-assessed when culture results are available. If the bacterial strains isolated are reported to be susceptible to the antimicrobial drug selected, no change in treatment plan is required. If one or more isolated strains are

Table 3
Drug table summarizing recommendations for the management of bacterial urinary tract infection in dogs and cats.

Drug (WHO category)[a]	Dose	Comments
Amikacin (CIA)	Dogs: 15–30 mg/kg IV/IM/SC every 24 h Cats: 10–14 mg/kg IV/IM/SC every 24 h	Not recommended for routine use but may be useful for treatment of multidrug resistant organisms. Potentially nephrotoxic. Avoid in animals with reduced kidney function. Other factors (e.g. low pH) can affect aminoglycoside activity, which should be considered. Care should be taken when using it in combination with nephroactive drugs (e.g. NSAIDs).
Amoxicillin (CIA)	11–15 mg/kg PO every 8–12 h	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. Ampicillin is used in susceptibility tests to predict activity of amoxicillin. Breakpoint for susceptibility testing is ≤0.25 μg/mL for systemic infections but a breakpoint of ≤8 μg/mL can be used for lower urinary tract infections owing to high urine concentrations. Not recommended for pyelonephritis or prostatitis.
Amoxicillin/clavulanic acid (CIA)	12.5–25 mg/kg PO every 12 h Note: dose of total product (amoxicillin + clavulanic acid)	Not established whether there is any advantage over amoxicillin alone for sporadic bacterial cystitis. Reasonable empiric choice for cystitis when regional susceptibility data support a high prevalence of resistance to amoxicillin but susceptibility to amoxicillin/clavulanic acid. Not recommended for pyelonephritis or prostatitis. Breakpoint for susceptibility testing is ≤0.25 μg/mL for systemic infections but a breakpoint of ≤8 μg/mL can be used for lower urinary tract infections owing to high urine concentrations.
Ampicillin (CIA)		Not recommended because of poor oral bioavailability. Amoxicillin is preferred. Ampicillin is used in susceptibility tests to predict activity of amoxicillin.
Cefazolin (HIA)	22 mg/kg IV ~30 min prior to the procedure.	Main use is for peri-procedure prophylaxis as a single pre-procedure dose. Cefazolin, at a breakpoint of ≤16 μg/ml can also be used to predict activity of oral cephalosporins.
Cefovecin (HP-CIA)	8 mg/kg single SC injection. Can be repeated once after 7–14 days.	Duration and spectrum are longer than is typically needed, so not recommended for routine use. Should only be used in situations where oral treatment is not possible. *Enterococcus* spp. are resistant. Pharmacokinetic data are available to support a duration of 14 days in dogs and 21 days in cats.
Cefpodoxime proxetil (HP-CIA)	Dogs: 5–10 mg/kg every 24 h PO Cats: no dose established.	More active than cephalexin or cefadroxil against Enterobacteriaceae when using the breakpoint of 2 μg/mL for interpretation. *Enterococcus* spp. are resistant.
Ceftiofur (HP-CIA)	Dogs: 2 mg/kg every 12–24 h SC Cats: no dose established.	Approved for treatment of bacterial cystitis in dogs in some regions. *Enterococcus* spp. are resistant.
Cefuroxime (HIA)	Peri-operative prophylaxis: 20–50 mg/kg slow IV	2nd generation cephalosporin that can be used peri-operatively. *Enterococcus* spp. are resistant.
Cephalexin, cefadroxil (HIA)	12–25 mg/kg PO every 12 h	Narrow-spectrum activity; not active against Enterobacteriaceae when using the current breakpoint of 2 μg/mL but CLSI has recently revised the breakpoint to <16 μg/ml, consistent with human medicine. *Enterococcus* spp. are resistant.
Chloramphenicol (HIA)	Dogs: 40–50 mg/kg PO every 8 h Cats: 12.5–20 mg/kg (to a maximum of 50 mg/cat) PO every 12 h	Reserved for multidrug resistant infections with few other options. Myelosuppression can occur, particularly in cats and with long-term (e.g. >28 days) therapy. Avoid contact by humans because of rare idiosyncratic aplastic anemia. Not a first line treatment for pyelonephritis or prostatitis.
Ciprofloxacin (HP-CIA)	25–30 mg/kg PO every 24 h	Sometimes used because of lower cost than veterinary fluoroquinolones. Lower and more variable oral bioavailability than approved veterinary fluoroquinolones. Difficult to justify over approved fluoroquinolones. Dosing recommendations are empirical and based on limited pharmacokinetic studies. No interpretive criteria are available for testing isolates from animals as CLSI recommends that human breakpoints not be used for testing canine isolates. Not recommended for prostatitis.
Doxycycline (HIA)	5 mg/kg PO every 12 h	Not excreted in urine at high levels but can achieve levels that are effective against some pathogens. Reserved for infections caused by pathogens that are resistant to drugs that are actively excreted in urine in active form. Care should be taken with administration recommendations in cats to reduce the risk of esophageal ulceration.
Enrofloxacin (HP-CIA)	5 mg/kg PO every 24 h (cats) 5–20 mg/kg every 24 h (dogs)	Excreted in urine predominantly in active form. Reserve for documented resistant infections but initial/empirical choice for pyelonephritis and prostatitis in dogs at the higher end of the dosing range. Not recommended for *Enterococcus* spp. Associated with risk of retinopathy in cats. It is recommended to avoid enrofloxacin in cats. If it must be used, a dose of 5 mg/kg per day should not be exceeded.
Fosfomycin (CIA)	40 mg/kg PO (with food) every 12 h	Should be reserved for multidrug resistant infections. Do not use in cats. Potential option for pyelonephritis and prostatitis, dosed every 8 h.
Imipenem-cilastatin (CIA)	5 mg/kg IV/IM every 6–8 h	Reserve for treatment of multidrug resistant infections, particularly those caused by ESBL-producing Enterobacteriaceae or *Pseudomonas aeruginosa*. *Enterococcus faecium* is inherently resistant. Recommend consultation with a urinary or infectious disease veterinary specialist or veterinary pharmacologist prior to use.
Levofloxacin (HP-CIA)	25 mg/kg PO every 24 h (dogs)	Sometimes used as a lower cost fluoroquinolone. Licensed fluoroquinolones should be used when possible. High oral bioavailability in dogs.
Marbofloxacin (HP-CIA)	2.7–5.5 mg/kg PO every 24 h	Excreted in urine predominantly in active form. Reserve for documented resistant infections but good first line choice for pyelonephritis. Considered first-line choice for infections that involve the prostate. Not recommended for *Enterococcus* spp.

Table 3 (*Continued*)

Drug (WHO category)[a]	Dose	Comments
Meropenem (CIA)	Dogs: 8.5 mg/kg SC/IV every 12 h (SC) or every 8 h (IV) Cats: 10 mg/kg every 12 h IV, SC, IM.	Reserve for treatment of multidrug resistant infections, particularly those caused by ESBL-producing Enterobacteriaceae or *Pseudomonas aeruginosa*. *Enterococcus faecium* is inherently resistant. Recommend consultation with a urinary or infectious disease veterinary specialist or veterinary pharmacologist prior to use.
Nitrofurantoin (IA)	4.4–5 mg/kg PO every 8 h	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 (HP-CIA)	Tablets: 2.5–7.5 mg/kg PO every 24 h Suspension (cats): 7.5 mg/kg every 24 h.	Excreted in urine predominantly in active form. Reserve for documented resistant infections but good first line choice for pyelonephritis. Considered a first-line choice for infections that involve the prostate. Not recommended for *Enterococcus* spp.
Pradofloxacin (HP-CIA)	Dogs: 3–5 mg/kg PO every 24 h.	Evidence is published regarding efficacy for treating bacterial cystitis in dogs and cats.
	Cats: 3–5 mg/kg once daily (tablets) or 5–7.5 mg/kg every 24 h (suspension)	Greater activity against some bacteria than older fluoroquinolones (enrofloxacin, marbofloxacin, orbifloxacin). Theoretically a good first line choice for pyelonephritis, especially in cats. Not recommended for *Enterococcus* spp.
Trimethoprim-sulfadiazine/Trimethoprim-sulfamethoxazole/Ormetoprim-sulfadimethoxine (HIA)	15–30 mg/kg PO every 12 h	Appropriate initial or empirical option. Concerns regarding idiosyncratic and immune-mediated adverse effects in some patients; however, this is most relevant with long-term therapy. If prolonged (>7 days) 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. Activity against *Enterococcus* spp. in urine is controversial and should be avoided.
	Note: dose of total product (trimethoprim + sulfadiazine)	Can be considered a treatment choice for prostate infections.

HP-CIA: highest priority critically important antimicrobial.
CIA: Critically important antimicrobial.
HIA: highly important antimicrobial.
IA: Important antimicrobial.
KCS: keratoconjunctivitis sicca.
CLSI: Clinical Laboratory Standards Institute.
ESBL: Extended spectrum β-lactamase.
[a] Drug category per World Health Organization guidelines.

not susceptible, the animal's response should be considered. If clinical cure is documented, it is acceptable to continue with the initial antimicrobial that was chosen. If clinical failure is documented, an antimicrobial change is indicated.

3) Long-term therapy is not automatically warranted for recurrent cystitis, even in dogs with underlying comorbidities such as diabetes mellitus, and this is especially true if recurrent disease appears to be caused by re-infection. Short (3–5 days) durations should be considered for re-infection. Longer courses (7–14 days duration) 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. In those situations, drugs that are ineffective against *Escherichia coli* in tissue (e.g. amoxicillin/clavulanic acid) should be avoided (Clinical and Laboratory Standards Institute, 2018).
4) Intravesicular administration of antimicrobials or biocides is not recommended.
5) Efforts should be made to identify and control underlying causes (e.g. control of endocrinopathy, management of micturition disorders).

Follow up

Clinical cure rates are poorly established for recurrent cystitis. Most monitoring is based on clinical response, as data in the expected or desired microbiological, cytological or hematological response to treatment are lacking.

1) When short (3–5 days) durations of treatment are being used, culture during treatment is not recommended. When longer durations of treatment are being used, the benefit of intra-treatment culture is unclear.
2) When longer durations of treatment are being used, urine culture is reasonable to consider after 5–7 days of treatment; however, the approach to a positive or negative result should be considered in advance. Positive cultures indicate the need for evaluation of compliance and further diagnostic testing, to determine why the bacterium has not been eliminated, not simply a change in antimicrobial, particularly if clinical cure has been documented. Negative results could be used to help determine when to stop therapy if a long course of treatment is being used, but are not a guarantee of microbiological cure.
3) Culture of urine specimens, ideally collected by cystocentesis, can be considered 5–7 days after cessation of antimicrobials in animals where clinical cure is documented. However, this should be used as part of the diagnostic process to help differentiate relapse, re-infection and persistent infection, and to guide potential future diagnostic testing, not as an indication of a need to treat. The presence of bacteriuria post-treatment should be approached as described under 'Subclinical bacteriuria'. If client compliance is deemed to have been adequate, referral to a specialist should be considered to explore reasons for microbial persistence or rapid re-infection.

Prevention

In women, prophylactic antimicrobial therapy regimens have been reported to decrease the symptoms of clinical recurrent cystitis, although recurrence rates can be as high as 95% once antimicrobials have been discontinued (Albert et al., 2004). A recent study reported a protective effect of daily antimicrobial

prophylaxis in healthy women, but a concurrent increase in antimicrobial resistance (Fisher et al., 2018). Balancing potential efficacy, resistance and adverse effect is a challenge, and there are no published studies in dogs or cats. Single nightly dose nitrofurantoin has been anecdotally used in dogs to prevent recurrent cystitis, but efficacy data are lacking. Furthermore, adverse effects of these drugs exist and there is concern for selection of resistant bacteria with protocols such as these.

Alternative approaches for prevention and treatment of recurrent cystitis that have been investigated in human beings as well as animal UTI models include the use of cranberry extract (McMurdo et al., 2009), cranberry juice (Stapleton et al., 2012), probiotics (Rodrigues et al., 2014; Stapleton et al., 2011), live biotherapeutic products (such as asymptomatic strains of *E. coli*) (Darouiche et al., 2005; Hull et al., 2000; Segev et al., 2018), vaccines (Billips et al., 2009) and various other alternative therapies, such as methenamine, D-mannose, and intravesicular or orally-administered glycosaminoglycans (Mansour et al., 2014). The efficacy of cranberry extracts to prevent UTI in women has been mixed. A recent meta-analysis concluded cranberry product administration may reduce the risk of recurrent UTI in healthy women, but also that larger and higher quality studies are needed (Fu et al., 2017). There has been limited study in dogs. In one study, cranberry extract prevented adherence of *E. coli* strains isolated from dogs to canine kidney cells, and six dogs with recurrent UTI treated with cranberry extract did not develop UTI when monitored for 2 months (Chou et al., 2016), but a placebo-treated control population was not studied. In another prospective, randomized, placebo-controlled study of 94 dogs with thoracolumbar disk herniation, cranberry extract did not appear to reduce the prevalence of bacteriuria, with six dogs in the placebo and 11 dogs in the cranberry extract group developing bacteriuria over a 6-week period (Olby et al., 2017). Live biotherapeutic products appear promising for treatment of recurrent cystitis, with a preliminary study reporting complete or nearly complete clinical cures in four out of nine dogs with recurrent cystitis in response to instillation of *E. coli* 2-12 (Segev et al., 2018).

1) Prophylactic antimicrobial therapy for dogs and cats is not recommended.
2) Treatment with short course (3–5 days duration) therapy ideally based on susceptibility testing is most appropriate to alleviate clinical signs, with a focus on clinical rather than microbiological cure.
3) There is insufficient evidence to recommend the administration of cranberry extract products and other alternative therapies at this time.
4) There is insufficient evidence to recommend administration of methenamine. Data from human medicine suggest it may be effective in some (but not all) human populations with recurrent cystitis (Lee et al., 2012), evidence of efficacy and safety in dogs and cats is lacking. Conversion to the active form (formaldehyde) requires low pH, which is not always assured in dogs and cat with recurrent cystitis.

Upper urinary tract infections (pyelonephritis)

Pyelonephritis is an infection of the renal parenchyma that can occur from ascending infection or bacteremia, with Enterobacteriaceae causing the majority of infections (Wong et al., 2015). In human medicine, acute pyelonephritis is classified as 'uncomplicated' or 'complicated'. Uncomplicated implies there is no underlying comorbidity; complicated suggested the presence of a systemic disease such as diabetes mellitus or neoplasia or an anatomical/obstructive disorder such as urinary stone disease or ectopic ureter.

Ascending infection can result from clinically evident lower urinary tract disease, but may also occur in the absence of an identified lower urinary tract infection or an apparent cause of bacteremia. Additionally, leptospirosis must be considered in endemic regions because the nephritis associated with leptospirosis can be considered with other bacterial causes of pyelonephritis (Sykes et al., 2011).

The incidence of pyelonephritis in dogs and cats is not well documented, in part because of difficulties definitively diagnosing this disease. Definitive diagnosis is difficult and signs attributable to pyelonephritis can be vague. As opposed to bacterial cystitis, where patient morbidity is relatively low, pyelonephritis can result in severe and rapid kidney injury. Thus, rapid diagnosis and treatment is important, and the implications of initial treatment failure are higher as compared with bacterial cystitis.

As an infection of renal tissue, serum/soft tissue antimicrobial concentrations are a key determinant of potential drug efficacy rather than urine concentrations.

Diagnosis

1) Definitive diagnosis of pyelonephritis is challenging. A diagnosis of acute pyelonephritis can be suspected based on positive aerobic bacterial urine culture when accompanied by systemic signs such as fever, lethargy, and/or polyuria/polydipsia; renal pain on abdominal palpation; laboratory findings of azotemia, cylindruria, and peripheral neutrophilia with or without left shift (in the absence of another identifiable cause). However, animals with acute pyelonephritis may be oliguric or anuric or have vague clinical signs. Imaging findings such as renal pelvic dilation and/or blunting of the renal papilla on ultrasound examination may be noted, but are non-specific (D'Anjou et al., 2011). Care should be taken not to over-interpret the relevance of renal pelvic dilation, since it can be present in normal animals and those with other renal diseases (D'Anjou et al., 2011; Jakovljevic et al., 1999).
2) Increased concentrations of biomarkers such as serum creatinine or serum symmetric dimethylarginine (SDMA) can also support the presence of renal injury (Dahlem et al., 2017) in association with bacteriuria, but are indicators of glomerular filtration rate and are not specific for bacterial pyelonephritis as the cause of kidney injury.
3) Culture and susceptibility testing should always be performed. Cystocentesis specimens should be used for culture.
4) Obtaining a urine specimen for cytology and culture by pyelocentesis should be considered, particularly if results of culture of a cystocentesis specimen are negative, or when a cystocentesis specimen cannot be obtained.
5) Blood cultures are recommended at the same time as urine cultures in immunosuppressed or febrile animals.
6) Interpretation of susceptibility data should be based on antimicrobial breakpoints for serum rather than urine drug concentrations. It is important that culture specimen submissions indicate that pyelonephritis is suspected to ensure that urine breakpoints are not applied.
7) If multiple organisms are isolated from urine, the suspected relative relevance of these should be considered. This assessment would include the bacterial species and colony counts.
8) Evaluation for leptospirosis should be considered in culture-negative dogs by use of serological testing and PCR (Sykes et al., 2011).

Treatment

1) Treatment should be initiated immediately, while awaiting culture and susceptibility results.

2) Initial treatment should involve antimicrobial drugs known to have local or regional efficacy against Enterobacteriaceae. If regional data are supportive, a veterinary fluoroquinolone or cefpodoxime are reasonable first choices. Cefotaxime and ceftazidime are options for IV administration.
3) If ascending infection is suspected, recently obtained urine culture results should be the basis of initial therapy (remembering that serum breakpoints must be considered). If hematogenous spread is suspected, initial therapy should be based on cultures of blood or the infected site, whenever available.
4) Oral antimicrobial therapy is recommended in animals that otherwise appear systemically well and have normal appetite. Intravenous therapy is recommended for animals that are dehydrated, hyporexic or anorexic, or lethargic. In humans, oral antimicrobial therapy for acute pyelonephritis was as effective compared to treatment with initial parenteral treatment followed by oral antimicrobial therapy (Hoberman et al., 1999; Strohmeier et al., 2014).
5) Culture and susceptibility data should be reviewed when results are received.
   a) If combination therapy was initiated empirically and the isolate is susceptible to both drugs, one might be discontinued if supported by evidence of clinical response.
   b) 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.
   c) If resistance is reported to both antimicrobials and clinical evidence of improvement is not evident, antimicrobial treatment should be changed to a drug to which the offending organism is susceptible *in vitro*.
   d) If resistance to the drug(s) that are used is reported but there has been good clinical response, continuation with the initial therapy could be considered, provided there are not other reasons (such as fluid therapy) that might explain clinical improvement. Otherwise, a change in antimicrobial is indicated.
6) Consultation with a specialist (veterinary clinical microbiologist, internist with infectious disease or nephrology/urology expertise and/or veterinary pharmacologist/pharmacist) is indicated with multidrug resistant organisms.
7) A diagnosis other than bacterial pyelonephritis should be considered if there is no improvement in systemic signs, hematology or serum biochemistry (e.g. azotemia, acute phase proteins) within 72 h of antimicrobial therapy and the results of culture and susceptibility indicate susceptibility to the antimicrobial used and there is confidence in client compliance. At that time, consideration should be given to a diagnosis of subclinical bacteriuria (with discontinuation of antimicrobial therapy) or for the presence of uncontrolled underlying factors (e.g. ureteroliths, neoplasia) that would need to be addressed to resolve the underlying infection.
8) Treatment for 4–6 weeks has previously been recommended for veterinary patients (Weese et al., 2011). However, the recommended duration of therapy for acute bacterial pyelonephritis in humans is 7–14 days (Gupta et al., 2011; Morello et al., 2016). In prospective studies, clinical and microbiological cures were not inferior when comparing 750 mg/day of IV levofloxacin for 5 days compared to 500 mg/day IV followed by oral levofloxacin for 7–14 days (conventional therapy) in humans (Ren et al., 2017). 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 Working Group recommends 10–14 days of treatment.

Follow up

A recheck examination that includes physical examination, serum creatinine concentrations, urinalysis and aerobic bacterial urine culture is recommended 1-2 weeks after cessation of antimicrobials. However, if clinical signs and azotemia have resolved, consideration has to be given to the clinical relevance of microbiological failure, as it may represent subclinical bacteriuria and not indicate a need for treatment. Re-isolation of the same bacterial species as that identified initially should stimulate consideration of reasons for potential persistence, including antimicrobial resistance, urolithiasis, anatomic defects or immune deficiency. Management of positive urine cultures in animals that have responded clinically and hematologically should be as per 'Subclinical bacteriuria'.

Bacterial prostatitis

Bacterial prostatitis is an uncommonly encountered problem in veterinary practices in some regions because of the high prevalence of castration in the canine population. However, it is second to benign prostatic hyperplasia/hypertrophy as a leading cause of prostatic disease (Polisca et al., 2016). Various bacteria can be involved, including a range of Gram-negative (e.g. *E. coli, Klebsiella, Pseudomonas, Pasteurella*) and Gram-positive (e.g. *Streptococcus, Staphylococcus*) species (Niżański et al., 2014). *Brucella canis* is potentially important zoonotic pathogen that can also be involved (Brennan et al., 2008).

The blood prostate barrier poses treatment challenges as it may limit penetration of antimicrobials into prostatic tissues, particularly in chronic prostatitis. While this barrier may be less effective in acute prostatitis (Barsanti, 2012), it is impossible to predict. Therefore, antimicrobials that are known to reach effective concentrations in the prostate should be used in all situations. Lipid soluble antimicrobials that are weakly alkaline with a high pKa are most likely to adequately cross the blood-prostate barrier (Niżański et al., 2014). Early work using dogs as a model for human disease indicated that trimethoprim (but not sulfonamides) had good prostate penetration (Baumueller and Madsen, 1977). If antibacterial activity is dependent on the synergism of the trimethoprim-sulfonamide combination, response may be low. However, a retrospective study in dogs provided low level evidence of comparable efficacy of trimethoprim-sulfonamides and enrofloxacin, with few adverse effects (Sefastsson et al., 2018). Macrolides and clindamycin are not active against the Enterobacteriaceae; therefore, they are not good empirical choices. Fluoroquinolones tend to be excellent drugs for Enterobacteriaceae and enrofloxacin has been shown to adequately penetrate the canine prostate (Dorfman et al., 1995). Chloramphenicol reaches prostate fluid concentrations that are only 60% of the plasma concentrations in dogs and it is doubtful that it can reach therapeutic levels in dogs. Tetracyclines (minocycline and doxycycline) reached levels in the canine prostate fluid that were <20% of the plasma concentration (Baumueller and Madsen, 1977; Fair, 1974) and are therefore not recommended.

Duration of treatment has not been adequately studied in dogs. Antimicrobial treatment durations of 4–12 weeks have been recommended (Niżański et al., 2014), but comparison of different durations has not been reported. In humans, 3, 4 and 6 weeks have been most widely reported, with a systematic review indicating that no conclusions can be drawn regarding differences between those durations (Perletti et al., 2013).

Diagnosis

1) An investigation for underlying bacterial prostatitis should be performed in every intact male dog diagnosed with bacteriuria or bacterial cystitis.

2) A full diagnostic examination, including physical examination, per rectum palpation of the prostate, complete blood cell count, biochemical profile, urinalysis and urine culture (collected by cystocentesis) should be considered.
3) Ultrasonographic evaluation of the prostate is recommended to characterize the size and structure of the prostate, to identify changes consistent with neoplasia (e.g. mineralization) or abscessation.
4) Cytological examination and aerobic bacterial culture should be performed on the third fraction of the ejaculate, fluid collected by urethral catheterization or per-rectum prostatic massage, or prostatic fluid collected by fine needle aspiration. The latter is particularly helpful when there is strong suspicion for prostatitis and the urine culture is negative for bacterial growth. Collection of ejaculated prostatic fluid may not be possible in dogs with acute prostatitis because of pain but may be successful in some cases, particularly with methods that can include sedation and analgesia. Oftentimes, a positive urine culture combined with clinical signs and ultrasonographic findings are used to make the diagnosis of bacterial prostatitis.
5) Culture of ultrasound-guided aspirates or prostatic tissue biopsies can be more specific than ejaculate fluid or fluid collected by prostatic lavage as contamination is less likely. These techniques should be considered when equipment and expertise are available. Prostatic aspirates and biopsies should also be submitted for cytological or histopathological examination in cases of concurrent neoplasia.
6) Culture of urine collected by cystocentesis can provide a reasonable estimate of the causative agent of prostatitis but discordance between urine and prostatic fluid culture results can occur (Black et al., 1998).
7) *Mycoplasma* and *Ureaplasma* culture could be considered but is of low yield because the incidence of infections caused by these organisms is low.
8) Quantitative culture of prostatic fluid can be performed; however, clear data are lacking for interpretation. Prostatic fluid is not expected to be sterile because of the potential for normal reflux of bacteria into the prostate, as well as lower urinary tract contamination during ejaculation or prostatic lavage. Prostatic fluid CFU counts can be high (e.g. 100,000 CFU/mL) in healthy dogs (Barsanti and Finco, 1986). It has been suggested that a 2-log difference between prostatic and urine CFU counts is indicative of bacterial prostatitis (Ling et al., 1983), but objective data are lacking.
9) Isolation of *Brucella canis* at any level of growth is significant, but serological testing is recommended if *B. canis* infection is possible because of laboratory biosafety hazards associated with isolation of this bacterium and the potential for false negative cultures. Testing for *B. canis* should be performed in any dog that is intended to be used for breeding.
10) Antimicrobial susceptibility breakpoints for serum, not urine, should be used because the concentration of the antimicrobial in the prostatic tissue is likely to most closely approximate that in the serum. However, not all antimicrobials penetrate the blood-prostate barrier equally, and this must be considered when selecting an appropriate antimicrobial.

Treatment

1) Prostatic abscesses should be drained because of the low likelihood of resolution with medical treatment alone. Surgical or ultrasound-guided percutaneous drainage can be performed (Boland et al., 2003). This should be performed after culture results are available, whenever possible, to facilitate proper peri-operative antimicrobial therapy. Concurrent with drainage, treatment as for chronic prostatitis should be administered.
2) Empirical treatment should target Enterobacteriaceae ideally with knowledge of local susceptibility trends. Administration of a veterinary fluoroquinolone should be considered while awaiting culture and susceptibility testing results, particularly if brucellosis is suspected.
3) Trimethoprim-sulfonamide has a spectrum of activity that includes a broad range of potential pathogens. While sulfadiazine does not reach high levels in prostatic tissue, low-level evidence indicated comparable efficacy to enrofloxacin with limited adverse effects and it is commonly used in some countries.
4) Clindamycin and macrolides can effectively penetrate the blood-prostate barrier, but should only be used based on culture and susceptibility test results, and not for empiric therapy because of lack of efficacy against Gram-negative bacteria.
5) The blood-prostate barrier reduces the penetration of many drugs, such as penicillins, cephalosporins, aminoglycosides and tetracyclines. This barrier is typically considered to be less intact in acute prostatitis; however, these drugs should be avoided, regardless of in vitro susceptibility data, particularly in cases of chronic prostatitis.
6) If a bacterial isolate that is resistant to fluoroquinolones, trimethoprim-sulfamethoxazole, clindamycin and chloramphenicol is present, consultation with a theriogenologist, veterinary microbiologist, pharmacologist or internist with expertise in infectious diseases or urology is recommended.
7) Ciprofloxacin should not be used because of the unpredictable bioavailability in dogs (Papich, 2012) and relatively poor prostate penetration compared to enrofloxacin (Albarellos et al., 2006; Dorfman et al., 1995).
8) Fosfomycin is an option for treatment of prostatitis caused by multidrug resistant Gram-negative organisms in people (Grayson et al., 2015), and while veterinary data are lacking, this drug (dosed every 8 h) could be considered for treatment of resistant Gram-negative infections.
9) Limited data are available to guide duration of treatment. Four weeks is typically recommended for acute prostatitis, with 4–6 weeks for chronic disease (Barsanti, 2012; Niżański et al., 2014). Shorter durations might be effective in acute cases that are castrated and where there is quick clinical response; however, objective data are lacking. A longer duration of treatment may be required in some chronic cases, particularly when abscessation is present or when castration is not performed (Cowan et al., 1991).
10) Castration should be recommended in dogs that are not intended for breeding. Castration does not alter the recommended antimicrobial drug choice or duration, but should be performed as early as is possible.
11) Other medical approaches to control underlying prostatic disease should be considered (e.g. finasteride, androgen receptor antagonists or GnRH agonists). These approaches are less successful when intraprostatic cysts or abscesses are present. Ultrasonographic re-evaluation of prostatic size and internal architecture is advised in dogs 8–12 weeks after treatment.
12) When initial treatment has failed and antimicrobial resistance or other correctable factors such as client compliance have not been implicated as the cause, resolution of infection is unlikely. In such cases, castration is strongly recommended, if not performed initially.
13) Poor initial response to therapy should lead to re-assessment of the diagnosis and if prostatitis is still suspected. Collection

of ultrasound-guided fine needle aspirate of prostatic cyst fluid or prostatic tissue core biopsy for culture and cytology or histopathology should be considered, and/or a BRAF test if not already performed. If further testing is not possible and prostatitis is still suspected, empirical change to a different antimicrobial can be considered because ejaculate culture does not always correlate with prostatic cyst fluid or prostate tissue core biopsy culture (Ling et al., 1990). A drug from a different drug class should be chosen if an empirical change is made.

14) In dogs with persistent prostatic abnormalities (e.g. prostatomegaly) but no clinical signs consistent with prostatitis, subsequent treatment should focus on treatment of episodes of cystitis that develop. This should be managed as described under 'Sporadic bacterial cystitis or "Bacterial prostatitis", with the goal being elimination of clinical signs.

Follow-up

1) Prostatic size should be monitored by ultrasound ± transrectal palpation.
2) Culture of prostatic fluid or urine can be performed during the course of therapy, but is not recommended. Clinical response and monitoring of prostatic size/architecture are better indicators of whether treatment is successful. Semen quality improves with resolution of bacterial prostatitis in most cases.

Subclinical bacteriuria

Subclinical bacteriuria is defined as the presence of bacteria in urine as determined by positive bacterial culture from a properly collected urine specimen, in the absence of clinical evidence of infectious urinary tract disease. Terminology such as 'urinary tract infection' or 'occult infections' have been used in reference to animals with positive bacterial cultures but no clinical signs of lower urinary tract disease (McGuire et al., 2002; Peterson et al., 2012); however, this terminology should be avoided. The term bacteriuria has been used to describe cases where bacteria are visible cytologically, irrespective of culture results (Way et al., 2013); however, diagnosis of bacteriuria should be based on culture (Nicolle et al., 2005). 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 (Forrester et al., 1999; O'Neil et al., 2013), but this has not been a consistent finding (McGuire et al., 2002). Poor agreement between cytological detection of bacteria and positive urine culture has been reported in dogs (McGhie et al., 2014; Peterson et al., 2012). Increased urine sediment red blood cell count is also not predictive of positive cultures (Forrester et al., 1999; O'Neil et al., 2013). Thus, cytological data are useful adjunctive data to assess animals with potential urinary tract disease but may not be highly predictive of culture results, infectious disease or correlate well with clinical signs of upper or lower urinary tract disease. Similarly, proteinuria is not predictive of subclinical bacteriuria.

Subclinical bacteriuria is not uncommon, even in individuals with no known predisposing factors. Rates of 2.1–12% have been reported in healthy dogs (McGhie et al., 2014; O'Neil et al., 2013; Peterson et al., 2012; Wan et al., 2014; Way et al., 2013), with higher rates (15–74%) in groups such as dogs with diabetes mellitus, morbidly obese dogs, puppies with parvoviral enteritis, dogs with acute disk herniation, chronically paralyzed dogs and dogs treated with cyclosporine or glucocorticoids (Baigi et al., 2017; Koutinas et al., 1998; Lusby et al., 2011; McGuire et al., 2002; Olby et al., 2017; Peterson et al., 2012; Torres et al., 2005). Study of subclinical bacteriuria has been limited in cats and the prevalence may be lower than reported in dogs; however, rates of 1–13% have been reported in healthy cats (Eggertsdóttir et al., 2011; Puchot et al., 2017; White et al., 2016). No evidence of an association between subclinical bacteriuria and risk of development of cystitis or other infectious complications has been reported in dogs or cats, although study has been limited. A study of 101 healthy female dogs identified bacteriuria in nine (8.9%) and found no association with subsequent cystitis development over a 3 month follow-up period (Wan et al., 2014). Bacteriuria was not associated with fever or survival in a study of paralyzed dogs (Baigi et al., 2017). Similarly, a study of older cats reported that of 256 urine samples evaluated from 67 cats, subclinical bacteriuria occurred in 10–13% of samples and subclinical bacteriuria did not adversely affect survival despite withholding antimicrobials (White et al., 2016).

In humans, there is abundant support that antimicrobial treatment is not needed for asymptomatic bacteriuria (the human analogue of subclinical bacteriuria), even in most compromised patients (Dalal et al., 2009; Harding et al., 2002; Trautner and Grigoryan, 2014). 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 and European Association of Urology guidelines on urological infections do not recommend treating asymptomatic bacteriuria in almost all patient groups (Bonkat et al., 2017; Nicolle et al., 2005). Exceptions are patients undergoing transurethral resection of the prostate and patients that will be undergoing urologic procedures that result in mucosal bleeding (Nicolle et al., 2005). Screening and treatment of pregnant women is recommended (Nicolle et al., 2005); 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 (Nicolle, 2015). 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 (Nicolle et al., 2005). 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 (Hartley et al., 2015; Lee et al., 2015; Leis et al., 2014). 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 (Nicolle, 2014). While treatment might eliminate the current bacteriuria event, recolonization often follows (Dalal et al., 2009). 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 (Dull et al., 2014). Further, two studies have reported significantly higher bacteriuria recurrence rates in women treated for asymptomatic bacteriuria compared to untreated controls (Cai et al., 2012; Cai et al., 2015). Treated women also had higher rates of antimicrobial resistance in *E. coli* isolated from subsequent UTI (Cai et al., 2015).

Identifying clinical signs of cystitis may be challenging in some animals (e.g. animals with paresis or whose owners are unobservant). However, there are similarities to some human populations (e.g. paralyzed individuals or those with dementia). In those populations, the presence of changes such as abnormal odor

or pyuria are not indications to treat (Hill et al., 2013) Therefore, clinicians must critically assess their (and the owner's) ability to detect clinical signs, along with the patient's clinical and laboratory results, but should not automatically assume that bacteriuria indicates cystitis (and a need to treat).

Diagnosis

1) There are few indications for culture of urine from animals that do not have lower urinary tract signs (Table 4). 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 comorbidities, particularly those with disease such as hyperadrenocorticism and diabetes mellitus, where subclinical bacteriuria is often reported (Forrester et al., 1999; McGuire et al., 2002). While study of the clinical implications of subclinical bacteriuria in animals is lacking, in humans, treatment of asymptomatic bacteriuria in patients with endocrinopathy and most other comorbidities is not recommended (Dalal et al., 2009; Georgiadou et al., 2015; Harding et al., 2002; Mody and Juthani-Mehta, 2014; Zalmanovici Trestioreanu et al., 2015). There is no evidence (or clear reason to suspect) that the situation would be different in dogs and cats. Situations where treatment of subclinical bacteriuria would be indicated are rare; therefore, testing should rarely be required.
2) A diagnosis of subclinical bacteriuria is made based on identification of bacteria by culture of urine collected via cystocentesis in an animal without clinical signs attributable to bacterial cystitis. While confirmation of bacteriuria through isolation of the same bacterial species in two subsequent samples is a requirement for diagnosis in humans (Nicolle et al., 2005), this still provides limited clinical guidance because there is rarely an indication to treat subclinical bacteriuria, regardless of the duration or persistence of bacteriuria.
3) Cystocentesis is the preferred method for urine collection and urine should not be collected by other methods unless there are contraindications to cystocentesis, as per 'Sporadic bacterial cystitis'.
4) Bacterial cell count, typically expressed as CFU/mL, cannot differentiate subclinical bacteriuria from bacterial cystitis. Subclinical bacteriuria 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 (Forrester et al., 1999) and there is no evidence that high CFU counts indicate a greater risk of disease development. Subclinical bacteriuria is also not defined by the presence or absence of pyuria on urine sediment examination.
5) Re-testing of bacteriuric animals is not recommended. If subclinical bacteriuria was identified initially, something that should be uncommon since testing is rarely indicated, re-testing is rarely indicated, regardless of whether treatment was provided. Consideration of potential reasons for bacteriuria is important and the patient should have a full evaluation if, for some reason, a urine sample from a clinically normal animal is cultured.

Treatment

1) Treatment of subclinical bacteriuria with antimicrobials is rarely indicated and is discouraged. In animals where it is unclear whether clinical signs are attributable to cystitis, a short course (e.g. 3–5 days duration) of antimicrobials as recommended for sporadic cystitis could be considered. If there is no clinical response, antimicrobials should be discontinued, as an infectious process is unlikely.
2) Treatment of animals with pyuria or other cytological abnormalities without lower urinary tract signs is not recommended. Previous guidelines (Weese et al., 2011) 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 cystitis is not recommended (Nicolle et al., 2005). There is currently no evidence in veterinary medicine that would indicate a different approach to that taken in humans.
3) The isolation of a multidrug resistant bacterial species should not affect the decision whether to treat subclinical 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, at which time treatment with routine antimicrobials may be more practical if such treatment becomes clinically indicated (e.g. if the animal subsequently develops cystitis).
4) Treatment of subclinical 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) In rare circumstances, treatment of subclinical bacteriuria may be considered if there is concern that there is a particularly high risk of ascending or systemic infection or that the bladder may be a focus of extra-urinary infection. Good data are lacking to define high-risk populations, treatment is rarely recommended in most compromised human population (Nicolle et al., 2005) and it is likely that there are few animals that actually fall into this category. Therefore, treatment on the basis of suspected high risk of complications should be used sparingly.
6) In patients that are unable to display clinical signs of cystitis (e.g. spinal cord injury), a clinical judgement must be made,

Table 4
Situations where urine culture may be considered in dogs and cats that do not have lower urinary tract signs.

Situations where screening may be indicated	Suspected pyelonephritis Investigation of the bladder as a source of bacteremia/septicemia Patients that are to undergo a surgical or minimally invasive procedure that will involve entering or transection of the urinary tract Dogs with suspected struvite urolithiasis
Situations where screening is sometimes performed but the relevance is unclear	Diabetic patients that are difficult to regulate or are ketoacidotic Animals with spinal cord disease that cannot reliably display evidence of lower urinary tract disease

ensuring that consideration of the need and potential adverse impacts (e.g. adverse drug effects, antimicrobial resistance) are balanced. Patients that are unable to display clinical signs of cystitis complicate decision-making, as determining what represents 'subclinical' is difficult. Many of these patients are also likely regularly or persistently bacteriuric, further complicating matters. In those patients, the presence of systemic signs (e.g. fever) would be an indication for treatment. The relevance of changes in urine appearance and odor (e.g. gross discoloration, malodor) to differentiate infection from subclinical bacteriuria is unclear. However, sometimes a short course of treatment (e.g. 3–5 days duration) could be considered for the quality of life issues if bacteriuria may be playing a role.

7) Treatment of subclinical bacteriuria caused by plaque-forming (*Corynebacterium urealyticum*) and urease-producing (e.g. staphylococci) organisms could be considered because of their associations with encrusting cystitis and struvite urolith formation, respectively (Bailiff et al., 2005; Biegen et al., 2013; López-Medrano et al., 2008; Raab et al., 2015). Because of the potential difficulties in treating these conditions, consideration of a single short course (3–5 days duration) of treatment, as per 'Sporadic bacterial 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. Continued treatment of subclinical bacteriuria with these strains is likely not warranted.
8) There is currently no evidence that screening bacterial isolates for urovirulence factors should impact decision-making for subclinical bacteria as there are currently no data that indicate isolation of a bacterial strain that possesses urovirulence genes is of greater clinical relevance to an individual patient or that treatment will reduce the risk of disease.
9) In some situations, imaging or other diagnostic modalities may identify lesions that indicate the need for treatment in animals without overt signs of lower urinary tract disease (e.g. emphysematous cystitis, bladder wall mass). For any patient, consideration of the totality of clinical, imaging and laboratory results is required to determine whether treatment is indicated, and whether antimicrobials are indicated as part of that. An individual tailored approach should be implemented on a case by case basis.
10) There is currently no evidence that use of adjunctive treatments (e.g. cranberry extracts or probiotics) for prevention of cystitis or subclinical bacteriuria is effective, but there is no contraindication to the use of treatments and supplements that are known to be safe.
11) If an animal that was recently diagnosed with subclinical bacteriuria subsequently develops signs consistent with cystitis or pyelonephritis, treatment designed to target the organism isolated while clinical signs were absent can be considered. However, the likelihood that a subsequent infection is caused by a previous bacteriuria isolate is not known and probably decreases with time from the last culture. Repeat culture is indicated to determine the optimal treatment. If bacteriuria with a multidrug resistant bacterial species was previously diagnosed, consideration should be given to treating with analgesics while awaiting culture results. If there is a need to treat empirically, empirical treatment as per 'Sporadic bacterial cystitis' (e.g. amoxicillin) is recommended in animals with bacterial cystitis. If pyelonephritis is suspected, treatment targeting the previously-identified resistant bacterial isolate should be considered, with a plan to de-escalate once culture results are available if a susceptible organism is identified.

Urinary catheters

Urethral catheterization is a common procedure in veterinary medicine and a critical component of the management of some patients. However, as a urethral catheter acts as a direct communication between the external environment and the bladder, catheterization is associated with an inherent risk of bacteriuria or bacterial cystitis.

The presence of a urinary catheter can predispose to infection as a result of ascending migration of bacteria into the bladder, either within the catheter lumen, or along the outer surface of the catheter. Intraluminal migration is facilitated through poor catheter management (e.g. open collection systems, failure to keep the collection bag below the level of the patient, contamination during catheter system maintenance). Extraluminal migration is thought to be the main route of infection in humans (Hooton et al., 2010). Contamination of the bladder can also occur during catheter placement or, less commonly, from bacteremia that results in bacteriuria.

Colonization of the urinary catheter or bladder can result in cystitis, subclinical bacteriuria or extra-urinary infection. In humans, catheter-associated bacterial cystitis are among the most common healthcare-associated infection, and result in significant patient morbidity, healthcare costs and occasionally mortality (Hooton et al., 2010). The causative bacteria commonly originate from the patient's own enteric microbiota, and the duration of catheterization is the most important risk factor for the development of infection. In addition to the local effects of bacterial infection, the bladder can be a source of systemic infection, and it has been estimated that approximately 15% of human hospital-associated bacteremia cases have their origin in the urinary tract (Bryan and Reynolds, 1984).

Comparable veterinary data on the impact of catheter-associated bacterial cystitis are lacking; however, it is probably lower than in humans because there are fewer catheterized veterinary patients and fewer patients that are catheterized for extended periods of time. The incidence of cystitis following urinary catheterization in dogs and cats is poorly characterized, in part because of the failure to differentiate subclinical bacteriuria and cystitis. Regardless, the prevalence of bacteriuria in catheterized dogs and cats is high (10–55%) (Bubenik and Hosgood, 2008; Bubenik et al., 2007; Hugonnard et al., 2013; Ogeer-Gyles et al., 2006; Ruple-Czerniak et al., 2013; Sullivan et al., 2010), with the majority of those cases likely representing subclinical bacteriuria. Differentiation of cystitis from subclinical bacteriuria is important because of the high incidence of subclinical bacteriuria, but the potential importance of bacterial cystitis.

1) Proper (aseptic) catheter placement and maintenance are critical.
2) Open collection systems should not be used (Hooton et al., 2010).
3) Urinary catheters should be inspected regularly for any problems that could predispose to infection (e.g. breaks, gross fecal contamination).
4) Routine catheter replacement to prevent bacteriuria or cystitis is not recommended.
5) The duration of catheterization should be as short as possible. The need for a urinary catheter should be re-evaluated regularly (at least daily, if not more frequently) and catheters should be removed as soon as they are deemed unnecessary. In humans, prompt catheter removal is considered one of the most, if not the most, important infection prevention tool (Tenke et al., 2014).
6) Intermittent catheterization could be considered in selected patients where repeated atraumatic catheterization is possible.

7) Routine cytological evaluation of urine is not recommended for detection of bacteriuria or bacterial cystitis. Pyuria, hematuria or cytological evidence of bacteria can occur in the absence of cystitis.
8) Urine culture is not recommended in the absence of clinical signs consistent with cystitis, pyelonephritis, or where the bladder is being investigated as a potential source of systemic infection.
9) Treatment of bacteriuria in the absence of clinical evidence of cystitis or pyelonephritis is not recommended.
10) Prophylactic antimicrobial therapy for prevention of cystitis in catheterized animals is not indicated.
11) The use of methenamine as a urinary antiseptic (Hooton et al., 2010) is not recommended.
12) There is currently no evidence that cranberry extracts or probiotics for prevention of catheter-associated bacterial cystitis are effective, but there is no contraindication to the use of treatments and supplements that are known to be safe.
13) Infusion of biocides or antimicrobials into the bladder via the catheter is not recommended.
14) Catheter removal or replacement is not required in animals with subclinical bacteriuria, considering bacteriuria is common and not predictive of cystitis. Further, changing catheters might increase the risk of infection from contamination or trauma during catheter replacement.
15) While urinary catheters coated with antibacterial substances such as silver or chlorhexidine may reduce bacterial colonization of the catheter and biofilm formation (Ogilvie et al., 2015; Segev et al., 2013), there is inadequate clinical evidence to support their use for prevention of catheter-associated bacterial cystitis.

Management of patients after urinary catheter removal

1) Culture of the catheter tip at the time of catheter removal is not recommended (Smarick et al., 2004). Colonization of catheter tips is common (e.g. up to 42–56% in dogs and cats) (Hugonnard et al., 2013; Smarick et al., 2004) and catheter tip culture results are not predictive of development of cystitis (Smarick et al., 2004).
2) Routine urine culture after catheter removal is not recommended; however, if specific aspects about the case indicate a need for culture, cystocentesis should be performed, whenever possible.
3) If clinical signs of cystitis develop after catheter removal, diagnosis should be performed as per 'Sporadic bacterial cystitis' (i.e. using cystocentesis, if possible).
4) There is no indication for routine (prophylactic) antimicrobial treatment following urinary catheter removal in an animal with no evidence of cystitis.

Catheterized animals with clinical signs of cystitis

1) Bacterial cystitis should be suspected in catheterized animals that develop lower urinary tract signs, yet such patients may not be easily identified (e.g. dogs with indwelling catheters for management of intervertebral disk disease). As such, infection should be suspected in all cases of fever of unknown origin or bacteremia with an unknown focus.
2) A sudden change in the character of the urine (e.g. odor, gross appearance) should prompt consideration of whether bacterial cystitis has developed. These changes are not necessarily indicative of bacterial infection and should prompt further investigation, not necessarily treatment.
3) Urine culture should always be performed if bacterial cystitis or bacteremia is suspected. If catheterization is still required and signs of bacterial cystitis are present, the recommended approach is to remove the catheter, collect urine by cystocentesis, then place a new catheter. If this is not possible, the catheter should be removed, a new catheter placed and urine collected from the new catheter for culture. The first 3–5 mL of urine collected should be discarded before collecting the urine specimen for culture.
4) Culture of the catheter tip at the time of removal is not recommended because of the potential for colonization of the catheter with various bacteria, as well as contamination during catheter removal.
5) Urine culture should never be performed on urine from the collection bag or other part of the urine collection system.
6) Treatment of catheter-associated bacterial cystitis is more likely to be successful if the catheter can be removed. The cost-benefit of removing or retaining the catheter should be considered in the context of management of the infection and the patient's underlying disease condition.
7) In uncommon situations where treatment is indicated, antimicrobials should be selected as per 'Sporadic bacterial cystitis'.
8) After clinically-apparent resolution of catheter-associated bacterial cystitis, if the catheter cannot be removed, it should be replaced with a new catheter, since colonization of the catheter is likely, even with clinically successful treatment.

Urological surgery, minimally invasive urological procedures and urologic implants

The number and type of minimally invasive urologic procedures have increased in dogs and cats over the last 5–10 years. Currently, procedures performed include cystoscopy, cystoscopic bladder biopsy, cystoscopy-guided laser lithotripsy for removal of bladder and urethral stones, urethrotomy and urethrostomy, injection of bulking agents for treatment of urinary incontinence, voiding urohydropropulsion, urethral stent placement, ureteral stent placement, subcutaneous ureteral bypass (SUB) placement, urodynamic procedures, and cystoscopic laser ablation for ectopic ureters. Potential sources of infection during urologic procedures are the skin, as well as the vaginal and rectal microbiota. Procedures may be complicated by the presence of active infection at the surgical site, infection of adjacent sites (e.g. prostate) or subclinical bacteriuria. The implications of infection may be high in some situations because of the potential for persistent colonization of devices such as stents. Detailed American and Canadian guidelines have been developed for use in human patients (Mrkobrada et al., 2015; Wolf et al., 2008). Veterinary evidence pertaining to this topic is lacking.

Current recommendations in humans are that patients should be screened for asymptomatic bacteriuria before urologic surgery is performed (Wolf et al., 2008). If urine culture yields significant bacterial growth or the presence of a colonized urolith is suspected, then treatment as per 'Sporadic bacterial cystitis' based on susceptibility test results is recommended to reduce bacterial counts before proceeding.

In addition to considering prophylactic antimicrobial therapy, careful attention should be paid to surgical techniques that reduce the risk of infection, including hair clipping, handwashing, the wearing of sterile gloves, proper skin antisepsis, ways to minimize procedure times, and maintaining sterility of introduced devices. Use of novel devices with silver alloy or antimicrobial coatings may also be effective.

Pre-operative screening

1) Bacterial culture of urine collected by cystocentesis is indicated prior to cystoscopic procedures or laparoscopic or open urologic surgery, when possible.

2) If significant bacteriuria is identified, treatment based on susceptibility result is indicated for 3–5 days duration immediately before the procedure to reduce bacterial counts.

Peri-operative prophylaxis

1) Antimicrobial prophylaxis should be considered for procedures that involve stone manipulation or open surgical procedures that involve the urinary tract *if* pre-procedure culture of a cystocentesis-collected urine specimen yields significant bacterial growth.
2) When antimicrobial prophylaxis is indicated, the antimicrobial (s) should be administered IV no more than 60 min before the start of the procedure and be re-dosed intra-operatively after two half-lives of the drug have passed (when applicable), in order to target the time that bacterial invasion is most likely to occur. Typically, this is until wound closure or completion of an endoscopic procedure.
3) An appropriate choice for peri-operative prophylaxis is a 1st or 2nd generation cephalosporin.
4) If the animal is already on a course of antimicrobials, that antimicrobial should be continued peri-operatively if it is appropriate. Otherwise, the drug should be discontinued or one of the drugs recommended above for peri-operative use should be added, depending on the need for ongoing treatment and drug interactions.
5) In the absence of complicating factors or infection, peri-operative prophylaxis should not continue beyond 24 h (Wolf et al., 2008).
6) If bacteriuria was identified prior to the procedure, treatment may need to be considered for a longer time period post-operatively than 24 h (e.g. 3–5 days), depending on the procedure.

Simple cystoscopic urologic procedures without stone manipulation

These include cystoscopy, bladder biopsy, injection of urethral bulking agents, urethral stent placement, urodynamic procedures, and cystoscopic laser ablation for ectopic ureter correction. Although Canadian guidelines suggest that pre-operative antimicrobial prophylaxis may reduce the chance of bacterial cystitis following endoscopic urologic procedures (Mrkobrada et al., 2015), a recent meta-analysis of antimicrobial prophylaxis following cystoscopy in humans concluded that antimicrobials should not be used to prevent UTI and asymptomatic bacteriuria in patients that undergo cystoscopy with sterile urine in an ambulatory setting (Garcia-Perdomo et al., 2015). Treatment of humans with single-dose ciprofloxacin before cystoscopy (Cano-García et al., 2016) or fosfomycin tromethamine immediately after cystoscopy (Jiménez-Pacheco et al., 2012) also did not reduce risk of UTI or bacteriuria. Another recent study showed no advantage of antimicrobial prophylaxis following cystoscopic ureteral stent removal (Abbott et al., 2016). A meta-analysis of antimicrobial prophylaxis following urodynamic procedures concluded that antimicrobials could reduce the risk of bacteriuria, but there was insufficient evidence that such treatment reduced the risk of symptomatic UTI, and that any benefits should be weighed against expense and risk of adverse effects (Foon et al., 2012). Treatment with prophylactic oral antimicrobials did not reduce the risk of symptomatic infection following stented urethral hypospadias repair in humans (Kanaroglou et al., 2013). Anecdotally, development of bacterial cystitis does not appear to be a common problem in companion animals when urological procedures are performed without peri-procedural antimicrobial prophylaxis. Moreover, if cultures of bladder wall are required, it would be ideal to obtain these specimens when the animal has not received antimicrobials. American guidelines suggest that human patients that undergo simple urologic procedures may benefit from prophylactic antimicrobial therapy if certain risk factors are present, which were advanced age, anatomic anomalies of the urinary tract, poor nutritional status, smoking, chronic glucocorticoid use, immunodeficiency, externalized catheters, colonized endogenous or exogenous material, distant co-existent infection, and prolonged hospitalization (Wolf et al., 2008). Whether some of these risk factors increase the chance of bacterial cystitis following simple urologic procedures in dogs and cats is currently unknown, but it would seem logical to use antimicrobials if colonized endogenous or exogenous material or distant co-existent infection are known to be present.

1) Peri-procedure antimicrobials are not recommended for cystoscopic procedures in animals without pre-existing bacteriuria.
2) If pre-existing bacteriuria is present, in addition to treatment for 3–5 days in advance of the procedure, a 1st or 2nd generation cephalosporin should be administered IV no more than 60 min before the start of the procedure, repeated every two drug half-lives (as needed) during the procedure, and not continued after the procedure unless clinical signs are still present. If signs continue despite antimicrobial use, the urine should be re-cultured; if negative, other causes for the clinical signs should be investigated (e.g. clipper burn, vestibulitis, vaginitis) and analgesics considered.

Procedures that involve urolith removal

These include voiding urohydropropulsion, and laser lithotripsy for removal of cystoliths and urethroliths. In human patients, there is evidence that periprocedural antimicrobials reduce the risk of bacterial cystitis following stone manipulation procedures (ureteroscopy and percutaneous nephrolithotomy) (Mrkobrada et al., 2015).

1) Antimicrobials are not indicated in all animals undergoing voiding urohydropropulsion.
2) If concurrent bacterial cystitis is suspected, this should be managed as per ‘Sporadic bacterial cystitis’.
3) In animals without lower urinary tract signs, it is ideal to obtain a culture 1 week prior to the procedure and treat patients with positive cultures, based on susceptibility results, for 3–5 days before the procedure, followed by administration of a 1st generation cephalosporin (i.e. cefazolin) IV no more than 60 min before the start of the procedure, repeated every two drug half-lives (as needed) and not continued after the procedure.
4) If the presence of uroliths colonized with bacteria is suspected, based on the presence of a urolith and a history of cystitis or bacteriuria, prophylactic antimicrobial administration is recommended. Treatment as per ‘Sporadic bacterial cystitis’ can be considered starting 3–5 days before the procedure, followed by administration of a 1st generation cephalosporin (i.e. cefazolin) IV no more than 60 min before the start of the procedure, repeated every two drug half-lives (as needed) and not continued after the procedure.

Open or laparoscopic surgery with urinary tract entry

These include ureteral stent or SUB placement, laparoscopic assisted cystotomy, percutaneously cystolithotomy and renal nephrolithotomy. Post-surgical bacteriuria following stent placement was documented in 31% of cats, but 13% of cats were reported

to develop bacterial cystitis >1 month after stent placement (Berent et al., 2014). It was unclear whether all of these cats had bacterial cystitis as opposed to subclinical bacteriuria. These cats were treated with peri-operative cefazolin followed by marbofloxacin for 2 weeks if previously instituted antimicrobial treatment was not being used for a pre-existing infection. Approximately 30% of cats treated with SUBs were reported to develop post-operative bacteriuria (Culp et al., 2016; Kopecny et al., 2017) and based on univariate analysis, post-operative antimicrobial administration appeared to reduce the risk of infection (Kopecny et al., 2017). Of 17 episodes of infection, 41% were associated with *Enterococcus* spp., with *E. coli* being the second most common isolate (Kopecny et al., 2017). Anecdotally, one site reported a higher prevalence of post-operative UTI in cats when an external urethral catheter was placed during SUB placement or in cats that had pre-existing bacteriuria before a SUB was placed (Berent, 2016). In human medicine, prophylactic antimicrobial therapy reduces the risk of febrile UTI following urinary tract surgery.

1) Peri-operative antimicrobial prophylaxis is indicated and should consist of a 1st or 2nd generation cephalosporin administered IV no more than 60 min before the start of the procedure, repeated every two drug half-lives (as needed), and not continued more than 24 h following the procedure. If post-operative infections with *Enterococcus* spp. are regionally important, consideration should be given to peri-operative treatment with an aminoglycoside in combination with ampicillin or cefazolin, if aminoglycosides are not contra-indicated. Prospective, randomized studies that evaluate the effect of post-operative antimicrobial use in cats following stent or SUB placement are required (Berent, 2016).

Medical dissolution of uroliths

Medical dissolution of uroliths is typically successful approach to struvite urolithiasis in dogs and cats (Houston et al., 2011; Lulich et al., 2013; Osborne et al., 1999) and is the recommended approach (Lulich et al., 2016). In dogs, unlike cats, almost all struvite calculi are infection-induced, usually by *Staphylococcus pseudintermedius* or, less commonly, by *Proteus mirabilis.* These bacteria have the ability to hydrolyze urea to form ammonia and carbon dioxide. This reaction increases the urine pH and makes ammonium available to form magnesium ammonium phosphate crystals.

Potential reasons for ongoing antimicrobial therapy during the dissolution period include the possibility that viable bacteria are released from within the urolith as it dissolves and because physical trauma to the bladder wall from the urolith could predispose to re-establishment infection. Counterpoints include a lack of evidence that the presumably small number of bacteria that could theoretically be released during dissolution pose a risk and the potential adverse effects of antimicrobial therapy (e.g. cost, adverse effects, antimicrobial resistance).

Limited data are available regarding antimicrobial therapy in conjunction with medical dissolution of struvite uroliths. Comparative data from human medicine are lacking because physical removal, not medical dissolution, is the standard approach. Various antimicrobial approaches have been used in conjunction with dietary management, including administration of antimicrobials throughout the duration of medical management (Bartges and Callens, 2015), for the first week of therapy(Calabrò et al., 2011) or for 1–4 weeks post radiographic resolution (Rinkardt and Houston, 2004). A small study of 12 dogs undergoing dissolution therapy and that received a 7 day course of enrofloxacin reported no development of subsequent infection or struvite crystals during the 75 day sampling period (Calabrò et al., 2011).

Diagnosis

1) Urine culture should be performed in all cases where urolithiasis is identified, even in breeds where non-infection-associated uroliths predominate (e.g. Dalmatians with urate uroliths) because of the potential for infection-associated uroliths in any animal, as well as the potential for secondary bacterial infection facilitated by the physical effects of any uroliths. For example, a urate stone could predispose to a *Staphylococcus* spp. infection and secondary struvite component to the urolith.
2) Culture of surgically-removed uroliths in dogs (which is recommended for very large struvite uroliths or those causing obstruction) should be performed if the urine culture is negative and the urolith is suspected (and then confirmed) to be composed of struvite. This is important for management purposes as sterile struvite uroliths (which are rare in dogs) are managed with dietary intervention and infection-induced struvite uroliths do not require further dietary therapy for urolith prevention. In the latter situation, once the nidus for the infection has been removed and clinical cure achieved, further antimicrobial therapy is not indicated.
3) Most uroliths removed from cats are sterile and the cost/benefit should be considered whether urolith cultures are warranted in this species.

Treatment

1) If evidence of bacterial cystitis is present, antimicrobial drug selection should be approached as per 'Sporadic bacterial cystitis', regardless of the known or suspected urolith type.
2) Urolith culture may not yield the same bacterium as urine culture (Perry et al., 2013). Treatment of bacterial cystitis should be based on pre-treatment urine culture and clinical response. If a bacterium isolated from urolith culture is resistant to the initial antimicrobial(s) selected, a change in antimicrobials is only indicated if there is poor response to treatment.
3) For infection-associated uroliths
   a If evidence of cystitis is present, seven days of treatment is recommended, ideally based on culture and susceptibility results. If culture results are not available, treatment should be approached as per 'Sporadic bacterial cystitis'.
   b If an infection-associated urolith is present or suspected but there is no evidence of bacterial cystitis, antimicrobials should be withheld until urine culture results are available. If a urease-producing bacterium (e.g. *Staphylococcus pseudintermedius*,*Proteus* spp.) is identified, antimicrobials should be administered; data regarding the duration of treatment during the dissolution protocol is has not be formally studied, but shorter courses are thought to be effective for dogs and antimicrobials need not be administered throughout the duration of the dissolution process.
   c If a non-urease producing bacterium (e.g. *E. coli*) is isolated and there is no evidence of cystitis, this should be approached as is described under 'Subclinical bacteriuria', and antimicrobial treatment is rarely indicated, unless prior to a minimally invasive or surgical removal (see previous section for recommendations).
   d If dissolution is not progressing as desired, urine culture should be repeated, along with concurrent patient re-assessment. If a urease-producing bacterial species is identified despite lack of clinical signs, treatment should be restarted based on susceptibility testing.
   e Limited data are available regarding the need for antimicrobials during dietary dissolution of struvite uroliths in animals

without evidence of ongoing bacterial cystitis. Evidence supporting a need for ongoing treatment is lacking.

4) For non-infection-associated uroliths
   a Seven days of treatment is recommended for animals with concurrent bacterial cystitis.
   b Further treatment should be unnecessary in the absence of lower urinary tract signs.

Conflict of interest

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