Urinary Tract Infection

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KEYWORDS

• Cystitis • Biofilm • Asymptomatic bacteriuria • Antibiotic

KEY POINTS

- Innate immune mechanisms are the primary defense of the lower urinary tract against symptomatic urinary tract infection.
- There are several options for in-house testing for urinary tract infection; however, many have been found to have drawbacks and must be carefully implemented.
- Asymptomatic bacteriuria is not an indication for treatment with antimicrobials and doing so may increase the risk of clinical infection as well as antibiotic resistance.
- Bacterial interference hold promise among several antimicrobial sparing treatments for urinary tract infection.

INTRODUCTION

Urinary tract infection (UTI) is a common diagnosis in companion animal practice. The incidence of UTI in the dog over its lifetime has been reported to be 14%[1] and in cats has been reported to be between 3% and 19%.[2–4] There are several factors thought to influence the risk of UTI in both species, including sex, age, comorbidities, and functional abnormalities of the lower urinary tract (LUT). There has been rising interest in characterizing the relationship of these risk factors to the development of UTI and bacteriuria. Point-of-care diagnostic testing for UTI has been evolving and improving therapeutic accuracy. A better understanding of the defense mechanisms of the LUT, the behavior of uropathogenic bacteria, and a growing awareness of the dangers of antimicrobial resistance have led to changes in the recommendations for diagnosis and treatment of UTI in dogs and cats.

Most of the UTIs in dogs and cats (~75%) involve a single agent, with *Escherichia coli* being responsible for up to half of the infections in dogs. This gram-negative organism is also the most common pathogen in cats (60%), with *Staphylococcus felis* being the most common Gram positive in that species.[5,6] A recent review from Italy found that gram-negative infections were more common than Gram positive and that there was more resistance to cephalosporins among these isolates than expected.[7]

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INNATE AND ADAPTIVE IMMUNITY OF THE BLADDER AND LOWER URINARY TRACT

The LUT has several mechanisms of defense against bacterial colonization. The innate immunity of the LUT is much better understood, and may be more important, than the adaptive immune functions. Prevention of ascending infection and mechanical removal of bacteria occurs in the ureters and bladder through the pulsatile flow of urine from the renal pelvis and the high shear flow of bladder voiding. In addition, there are several antimicrobial peptides that are expressed in the LUT, some in response to bacterial presence such as lipocalin-2, which prevents bacterial access to important mineral stores. The activation of the complement cascade and recruitment of neutrophils are also important parts of the LUT defenses. There is some evidence that if the host response is too vigorous and the development of inflammation too severe, there can be enough mucosal injury to take an acute UTI to a chronic state of inflammation and recurrent infections.[8,9] Immunocompromised mice that cannot mount a lymphocytic response in the LUT are also resistant to development of chronic cystitis. The addition of nonsteroidal antiinflammatory drugs (NSAIDs) in immunocompetent mice with recurrent UTI has shown to reduce this risk, even in animals with significant tissue injury.[10]

PATHOPHYSIOLOGY OF BACTERIAL CYSTITIS

The primary source of bacteria invading into the LUT is the colon and skin. The proximity of the rectum to the vulva makes this more common in female dogs and cats than in males. As in humans, the most common bacteria isolated from UTIs in the dog is *E coli*, followed by *Staphylococcus* species, *Proteus*, and *Klebsiella*. *Enterococcus* is often found as well, but most commonly as a secondary organism and will likely be cleared with treatment of the primary infection. Cats with UTI are primarily infected by *E coli*, followed by *Enterococcus faecalis* and *S felis*.

Bacteria in the LUT primarily exist in 2 forms, the planktonic state and the biofilm, which are phenotypically distinct and have differing host interactions and effects. Planktonic bacteria are free swimming in the urine and not adhered to any surface. They are generally more susceptible to many of the bladder defense mechanisms as well as antimicrobials but they also express different types of pili or fimbriae that facilitate adherence to inert and biological surfaces. Biofilms are structured communities of microorganisms within an adherent gel-like polymer, secreted by the organisms themselves.[11] They can form on the urothelium of the LUT or on inert surfaces such as urinary catheters and surgical implants. Biofilms are a frequent source of recurrent UTI in humans with indwelling catheters, and they present a challenge in dogs and cats with ureteral stents and subcutaneous ureteral bypass systems. The biofilm provides protection from antimicrobial substances through several mechanisms including decreased penetration, slow growth state of the bacteria, alterations in gene expression that confers resistance, and antibiotic binding/inactivation by polysaccharides in the matrix.[11,12]

Biofilms on inert surfaces begin with the formation of a “conditioning film” of components within the urine such as proteins and fibrinogen, which provide receptor sites for bacterial adhesins to attach. The bacteria sense the presence of an inert or biological surface through alterations in the concentration gradients of released signal molecules as they near it. A reversible adhesion of the bacteria occurs when the surface is encountered, which becomes irreversible with the formation of the biofilm structure. The biofilm is around 10% to 25% bacteria and 75% to 90% polysaccharide and water matrix with nutrient transport channels.[11]

The most widely studied bacterial biofilms in the urinary tract are those produced by uropathogenic *E coli* (UPEC). In the bladder, these bind to uroepithelial cells via uroplakins and $\alpha_3\beta_1$integrins, which triggers neutrophil influx into the bladder lumen.

The host responds to interactions of the superficial epithelium with bacterial Type 1 fimbriae by triggering exfoliation of the epithelial cell with the attached bacterium and subsequent removal with the next urination. Some UPEC survive this defense mechanism by moving intracellularly and replicating to form intracellular bacterial communities. These can lay dormant or release back into the urine to resume a planktonic state and start the cycle over again. These IBCs survive by producing toxins and proteases that release nutrients from host cells and siderophores to retrieve sequestered iron stores as well as by inducing antimicrobial efflux pumps. The bacteria are safe from antimicrobial exposure but can trigger an innate immune response that involves expulsion of the organism by the host cell.[9] Some UPEC have the ability to establish deeper colonies in the bladder interstitium called quiescent intracellular reservoirs where they can stay dormant for months before reactivation. Some bacteria, such as*Proteus spp*., will create a crystalline biofilm structure by producing urease and inducing struvite precipitation around the organism.[9]

RISK FACTORS

Whatever the organism, its ability to gain entrance to the LUT depends on an increased affinity for the environment of the bladder or a weakened host defense (**Box 1**). As noted earlier, female dogs and cats are at increased risk. One study in cats found females were 3.5 times more likely to develop an UTI than males. Several studies demonstrated an increased risk with increasing age and decreasing body condition score.[2,13,14] The inability to completely empty the bladder during micturition due to neurologic disease,[15]presence of urolithiasis, urinary incontinence, and immunosuppression have all been implicated as increasing risk of UTI in dogs and cats. Glucosuria has been shown to predispose dogs to emphysematous cystitis, a severe bladder infection with gas-producing organisms, but not to other types of UTIs.[16]

It has been a long held belief that decreased urine osmolality (ie, lower urine specific gravity) increased the risk for UTI due to dilution of substances that made urine a harsh environment for bacteria to grow. However, in recent years, this has been called into question because studies in cats have been unable to show a correlation with either clinical UTI or subclinical bacteriuria (SCB).[13] Dogs with a decreased urine specific gravity associated with hypercortisolism or diabetes mellitus did not seem to have an increased risk of UTI compared with those with more concentrated urine.[17] One recent in vitro study did note an increased ability to grow *E coli* in dilute urine,

Box 1
Identified risk factors for urinary tract infection and asymptomatic bacteriuria in dogs and cats

A list of some of the risk factors identified in dogs and cats for UTI and ASB.
- Female sex (D, C)
- Increased age (D, C)
- Decreased body condition score (D, C)
- Anatomic abnormality of the LUT (D, C)
- Functional abnormality of the LUT (D, C)
- Inability to empty the bladder (D, C)
- Urinary incontinence (D)
- Urolithiasis (D, C)
- Chronic kidney disease (D, C)
- Hyperthyroidism (C)
- Recent antibiotic use (D)
- Immunosuppression (D)

Abbreviations: C, cat; D, dog.

particularly if the urine was of acidic or neutral pH.[18] Further investigation is needed to determine the properties of urine that are most important as defenses against clinical UTI in the cat and dog.

The presence of a comorbidity may increase risk of UTI or SCB. In a recent study, among 194 cats with a positive urine culture, 78% had a comorbidity such as hyperthyroidism or chronic kidney disease (CKD). This study also found that cats with comorbidities were more likely to have SCB and those that were otherwise healthy were more likely to demonstrate clinical signs of infection.[4] The type of bacteria was also influenced by the presence of comorbidities. Healthy cats tended to have more *Staphylococcus* and *Streptococcus spp*. growth, whereas the cats with other systemic disease had more frequent *E coli* growth. There is some evidence that cats with CKD may have a higher incidence of SCB; however, this needs to be investigated further.[14] One study found that 17% of dogs with CKD had a positive urine culture, and of these, 45% were asymptomatic. It has been reported that in the healthy dog population, 2% to 9% of dogs have SCB, so it seems that CKD is associated with increased risk of SCB in dogs.[19] Whether this also indicates an increased risk for UTI has not been fully determined.

There is little information regarding the risk of UTI or SCB in dogs and cats that are treated with immunosuppressive drugs. Cyclosporine was shown to increase the incidence of SCB but not UTI in dogs treated for dermatologic disease with or without glucocorticoid therapy.[20] A similar study in cats found no association of glucocorticoid treatment, with or without cyclosporine, with either SCB or UTI.[21] It is not known whether the immunosuppression in the dogs prevented clinical signs of UTI by reducing the inflammatory response in the bladder or whether there were truly fewer uropathogenic colonizations. Anecdotal evidence suggests an increased risk of fungal cystitis, but the literature is limited to case reports.

SUBCLINICAL BACTERIURIA

There has been increased attention paid to what was once referred to as “occult UTI” but is now recognized as a subclinical bacteriuria. It has been recognized that the LUT is not a sterile site, and the urinary microbiome has begun to be defined in the dog;[22] however, most culture techniques of clinical urine samples are not sensitive enough to detect its components. Beyond the microbiome, there are a subset of dogs and cats that have a positive urine culture but do not have clinical signs of disease. In vitro and in vivo studies suggest that the host may have a genetic predisposition to a low response of the innate immune system to some of these bacterial strains.[23] Asymptomatic bacteriuria in humans is defined as the presence of bacteria with or without pyuria and lacking clinical signs associated with UTI, such as stranguria, pollakiuria, or suprapubicpain.[24] Standard of care is not to treat these patients with antimicrobial therapy unless they are pregnant or having invasive urinary procedures performed. There is strong evidence that the treatment of SCB does not decrease, and may increase, the risk of clinical UTI. It also promotes the development of antimicrobial resistance at a time when this is becoming a globally recognized problem.[25] Despite these guidelines, a recent study found that 17% of human hospital in-patient prescriptions of antimicrobials were for the treatment of SCB.[24]

The veterinary guidelines on treatment of UTI in cats and dogs indicate that SCB should not be treated.[26] The definition of SCB in dogs and cats has been under some debate. The potential for an owner to miss signs of discomfort and the subtlety of some clinical signs may lead to underdiagnosis of true UTI. In addition, there is a subset of patients, such as those with neurologic disease, which may not have enough

sensory or motor function to display such clinical signs as stranguria or pollakiuria. It has been argued that the presence of pyuria should be considered a "clinical sign" in patients with otherwise asymptomatic bacteriuria and that these cases be treated as UTIs. On the other hand, there is currently no evidence that those dogs and cats with pyuria and bacteriuria that go untreated will develop worse outcomes, even in the presence of comorbidities such as diabetes mellitus or CKD.[2,4,27] A recent study indicated that treatment of UTI in dogs was the source of approximately 12% of oral antibiotic prescriptions in veterinary practice in the Netherlands.[28] With more attention to the recommendation to withhold treatment of SCB, and a better understanding of the drawbacks associated with unrestrained antibiotic use, the veterinary community has a chance to reduce the risk of antimicrobial resistance development.

CLINICAL SIGNS AND DIAGNOSTIC TESTING

A thorough history is important when assessing a dog or cat for UTI. The most common clinical signs associated with UTI are pollakiuria, stranguria, and hematuria. Fever is rarely found unless the animal has prostatitis or pyelonephritis. It is important to distinguish pollakiuria (small frequent urinations), in which the inflamed bladder will become painful with even small amounts of distension, and behavioral marking, in which the animal can hold urine and fill their bladder for an appropriate amount of time between urinations. Patients may exhibit discomfort on palpation of the bladder or around the kidneys or prostate if they have pyelonephritis or prostatitis associated with the UTI. Many dogs and cats will overgroom their genitalia or caudal abdomen when an UTI is present, potentially contributing to irritation of the penis or vulva that may be related to the underlying infection.

Diagnostic testing for UTI starts with a complete urinalysis, including specific gravity, urine chemistry, and wet-mount, unstained sediment examination under microscopy. The individual parts of the urinalysis have variable values in detecting an UTI in small animals. Urine specific gravity has not been shown to be a reliable indicator of an UTI in the cat[13] nor is it cost-effective to reflexively perform cultures on dilute dog urine if pyuria is not detected.[29] The urine dip strips used in evaluating urine chemistry are less accurate in detection of UTI in small animals than in humans. The nitrite test pads on some urine dip strips test for the presence of nitrate-converting Gram-negative bacteria in human urine. Unfortunately, the test is not reliable in companion animals. The leukocyte esterase test pad detects esterases in granulocytes; however, there is a high false-negative rate in dogs and a high false-positive rate in cats.[30]

The urine sediment evaluation is the most valuable portion of the urinalysis in detecting an UTI in the dog and cat. The combination of pyuria (>3–5 WBC/hpf) and bacteriuria on a urine sediment leads to a high index of suspicion for UTI. Unfortunately, the detection of bacteria on unstained wet-mount sediments is fraught with problems. The modified Sternheimer-Malbin urinary stain (Sedi-Stain, Becton Dickinson) is useful to highlight red and white blood cells and casts; however, it only stains dead bacteria, and bits of debris can be mistaken for organisms.[31] Several studies have found that examination of wet-mount preparations in both dogs and cats will overestimate the presence of bacteria in a urine sample. Gram staining and Wright-Giemsa staining of dry-mount preparations were found to have a higher specificity and positive predictive value in both dogs and cats.[32] In another study, the wet preparations of cat urine were found to have a sensitivity of 76% and specificity of 57%, whereas Wright-stained preparations had a sensitivity of 83% and a specificity of 99%.[31] In cats, it seems there are fewer false negatives than false positives using wet-mount, unstained

preparations.[33] In dogs, wet-mount preparations were found to be inferior to Gram stain preparations, with a specificity of 66% versus 100%. Similar to the studies in cats, the wet-mount preparations had a 77% sensitivity, whereas the Gram-stained samples had a 96% sensitivity.[34] Although Wright-Giemsa and Gram staining of samples takes more time than preparing an unstained sample, it may reduce unnecessary culture and/or prescribing of antimicrobials in both dogs and cats.

The veterinary community has become more aware of the need for a reliable, rapid, and cost-effective point-of-care test for UTI in dogs and cats beyond the urinalysis. Several of these "bedside" diagnostics were developed for use in humans, and some have been investigated for use in dogs and cats. One test (AccutestUriscreen, Jant Pharmaceuticals), based on the presence of catalase in host cells as well as in many uropathogenic bacteria, was found to have an overall sensitivity of 89% and specificity of 71% in dogs and cats; however, it was still out-performed by the stained urine sediment examination.[35] A rapid immunoassay that differentiated between Gram-positive and Gram-negative bacteria in urine was evaluated in the dog and cat (RapidBac Vet, Silver Lake Research Corp).[36,37] It was found to have a 97% sensitivity and 99% specificity in dogs and a 79% sensitivity and 98% specificity in cats. The ability to determine gram-stain status of the bacteria is helpful to the clinician when choosing an appropriate antimicrobial without the benefit of a culture and antibiotic sensitivity profile. This diagnostic test may be useful in determining whether to perform a urine culture, especially in patients with sterile inflammatory urinary tract disease, such as cats with feline idiopathic cystitis.

Performance of in-house culture may also improve the ability of veterinarians to more accurately and cost-effectively diagnose and treat UTIs in dogs and cats. A urine culture paddle system (UriCult, LifeSign) was evaluated in dogs and cats and was noted to have a sensitivity and specificity of 89% to 97% and 99%, respectively for detection of bacteriuria; however, pathogen identification was only 76% accurate. It was also less accurate in samples with a low bacteria count. The investigators concluded the system may be of use but that the 24-hour wait time for test results was still not ideal.[38] Finally, a divided plate culture system (Flexicult Vet, Statens Serum), was evaluated on dog and cat urine samples.[39,40] Two studies found that it was highly sensitive and specific for detection of bacteriuria (sensitivity of 83% and specificity of 100%); however, the species identification accuracy was only 53% and highly depended on observer training. As with other culture systems, the delay in determining the presence of bacteria is less cost-effective if the test is unable to accurately identify the organism or determine its antimicrobial susceptibility. It is also important to remember that the accuracy of a test somewhat depends on the index of suspicion when performing it.

UNCOMPLICATED URINARY TRACT INFECTION

An UTI with clinical signs is generally considered "simple uncomplicated" or "complicated". Simple uncomplicated UTI is defined as occurring in an otherwise healthy patient with fewer than 3 episodes per year, no recent history of antimicrobial use, and a lack of underlying anatomic abnormalities of the LUT. Based on International Society for Companion Animal Infectious Disease (ISCAID) guidelines, the diagnosis of uncomplicated UTI includes the presence of clinical signs and a urinalysis with pyuria and bacteriuria. The guidelines recommend a quantitative urine culture be performed with suspected simple uncomplicated UTI.[26] Cultures should be performed on samples collected via cystocentesis or sterile catheterization. Free catch samples are only of value if the culture is negative. ISCAID guidelines recommend initial treatment of simple

uncomplicated UTI be with amoxicillin or trimethoprim-sulfonamide for 7 days.[26] Little additional intervention is needed if clinical signs resolve during treatment.

COMPLICATED URINARY TRACT INFECTION

Complicated UTI involves an anatomic or functional problem with the LUT or a comorbidity that will increase the risk of UTI in a patient, including recent antibiotic use. Recurrent UTI is defined as 3 or more UTIs in a 12-month period and is generally classified as either relapse or reinfection. Relapse is infection with the same organism within 6 months of a treated UTI, either because there is continued exposure to that particular organism or because there is a nidus of infection that has not been cleared or addressed. Reinfection is the recurrence of an UTI with what is presumed to be a different organism and is likely due to host factors such as impaired immune defenses or increased risk of infection. These can be difficult to distinguish, especially if the same species of bacteria is always present. Evaluation of the susceptibility pattern can help, but there can be drift in the susceptibility over time depending on selection pressures on the bacteria.[26] Few practitioners perform the DNA analysis that will verify reinfection with the same strain of bacteria.

The ISCAID working group recommends a urine culture on all patients with a complicated UTI.[26] In addition, an evaluation of the underlying comorbidities or functional/anatomic abnormalities should also be undertaken to determine if they are correctable. Improved control of hyperadrenocorticism, correction of ectopic ureters, and medical management of urinary incontinence can all decrease the frequency of complicated UTI. If the underlying cause is not apparent, imaging and potentially cystoscopic evaluation may be needed to find the abnormality.

Treatment of a complicated UTI should be delayed until a culture and antibiotic susceptibility evaluation is completed, if possible. This will help avoid development of resistance. Symptomatic treatment with NSAIDs or other pain control may be needed to bridge this time and keep the patient comfortable. If an antibiotic must be started before the results are reported, it is advised to choose either amoxicillin or trimethoprim-sulfonamide, as for a simple uncomplicated UTI. Some classes of drugs are present in higher concentrations in the urine than in the plasma. When choosing from the antibiotics that the bacteria are susceptible to, these should be given greater consideration, because the concentrations that the bacteria are tested against are related to plasma levels of the drug, not the urine concentration, and there is a significant difference, particularly with penicillin and fluoroquinolones. This can be especially important in cases of resistant bacterial UTI, where an intermediate susceptibility to one of these drugs may mean susceptibility at the levels achieved in the urine. Generally, treatment of complicated UTI is for 4 weeks. There is little evidence of the use of antibiotics flushed into the bladder as a treatment for bacterial UTI; however, it may be part of treatment for fungal UTI.

Monitoring of treatment of complicated UTI is important and consists of a urine culture 7 days after starting antibiotic therapy and 1 week after completing it. Treatment failure indicates a need for additional diagnostic investigation, as long as client (and patient) compliance have been established. It is not appropriate to simply choose a more broad spectrum antibiotic without looking into why the bacteria failed to clear when it was susceptible in vitro.

PREVENTION

The most important part of preventing an UTI is to eliminate predisposing and complicating conditions. In some patients, this is not possible, and clinicians must consider

options for preventing infection. These include prophylactic antibiotics, nonantimicrobial inhibitors of infection, and the introduction of competitive, nonpathogenic bacteria.

Prophylactic Antibiotic Therapy

Few studies have evaluated the effectiveness of continuous low dose or pulse antibiotic therapy for the prevention of UTI in dogs and cats. One study compared the use of a short-acting (cefazolin) and long-acting (cefovecin) cephalosporin perioperatively on dogs undergoing hemilaminectomy on the incidence of postoperative UTI. No difference was found between the 2 groups.[41] Current ISCAID guidelines do not recommend the use of low dose or pulse antibiotic prophylaxis in dogs and cats for prevention of UTI.[26]

Cranberry

Type A proanthocyanidins are a class of chemicals found in cranberry extract. They have been demonstrated in vitro to inhibit the *E coli* P fimbriae adherence to the uroepithelium.[42] This has been shown to be effective against *E coli* isolated from dogs and prevents attachment to canine uroepithelium; however, in vivo efficacy has been disappointing.[43] In a recent study evaluating the use of cranberry extract versus placebo in dogs with thoracolumbar disc herniation, no difference in the incidence of UTI was found; however, there was a suggestion that antiadhesion activity in the urine may have a protective effect.[43] Similar results have been found in people with recurrent UTI.

Mannose

E.coli that are pathogenic to the urinary tract (UPEC) express type 1 pili, which have a fimbriae H (FimH). This mediates the adherence of the bacterium to the uroepithelium via the oligomannosides of uroplakin1alectin. R-D mannosides block the adhesion of FimH in both the urothelium and the endometrium in animal models and is well tolerated. Although there are no randomized controlled trials in dogs or cats, such studies in people have had promising results.[42]

Probiotics

Women with UTI have a very different vaginal microbiome from those without one. In people, the use of probiotics to “normalize” the vaginal flora has proved successful in managing chronic and recurrent UTI. However, this approach does not seem to be as successful in dogs and cats. It may be due to the similarity of the vaginal microbiome in dogs with and without UTI. The maintenance of a healthy LUT and prevention of UTI in the dog is likely less dependent on the vaginal flora.[44] Probiotics have not been extensively evaluated in dogs or cats as a preventive measure for UTI; however, this evidence suggests they may be less useful than in people.

Bacterial Interference

Several strains of *E coli* isolated from chronic subclinical infections have been evaluated for protection against UPEC strains in animal models and in humans. There is evidence that in people, deliberately induced bacteriuria with these nonpathogenic strains may protect patients with incomplete bladder emptying from recurrent UTIs.[45] It is thought that these low-virulence nonpathogenic bacteria compete with and decrease the risk of colonization with more pathogenic organisms, although the mechanism is undetermined.[5] One study evaluated the effect of *E coli* 2 to 12 strain in 9 dogs with recurrent UTI. Four of these dogs achieved clinical cure of active infection and 3 of those had no recurrence of UTI. The biggest challenge in the use of this

therapy is maintaining the bacteria in the bladder once it is healthy.[46,47] Further investigation of this novel therapy in dogs and cats with recurrent UTI is warranted.

SUMMARY

There are new paradigms in the way we define, diagnose, and treat UTI in dogs and cats. The need for antibiotic stewardship and the recognition of SNCB in our patients is driving much of this change. New findings about the host response to colonization and better understanding of the planktonic and biofilm states of bacteria have revealed potential new antibiotic–sparing options for the future.

REFERENCES

1. Ling GV. Therapeutic strategies involving antimicrobial treatment of the canine urinary tract. J Am Vet Med Assoc 1984;185(10):1162–4.
2. White JD, Stevenson M, Malik R, et al. Urinary tract infections in cats with chronic kidney disease. J Feline Med Surg 2013;15(6):459–65.
3. Vapalahti K, Virtala AM, Joensuu TA, et al. Health and behavioral survey of over 8000 finnish cats. Front Vet Sci 2016;3:70.
4. Dorsch R, von Vopelius-Feldt C, Wolf G, et al. Urinary tract infections in cats. Prevalence of comorbidities and bacterial species, and determination of antimicrobial susceptibility to commonly used antimicrobial agents. TierarztlPraxAusg K KleintiereHeimtiere 2016;44(4):227–36.
5. Olin SJ, Bartges JW. Urinary tract infections: treatment/comparative therapeutics. Vet Clin North Am SmallAnimPract 2015;45(4):721–46.
6. Lund HS, Skogtun G, Sorum H, et al. Antimicrobial susceptibility in bacterial isolates from Norwegian cats with lower urinary tract disease. J Feline Med Surg 2015;17(6):507–15.
7. Rampacci E, Bottinelli M, Stefanetti V, et al. Antimicrobial susceptibility survey on bacterial agents of canine and feline urinary tract infections: weight of the empirical treatment. J Glob Antimicrob Resist 2018;13:192–6.
8. O'Brien VP, Hannan TJ, Schaeffer AJ, et al. Are you experienced? Understanding bladder innate immunity in the context of recurrent urinary tract infection. CurrOpin Infect Dis 2015;28(1):97–105.
9. Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol 2015;13(5):269–84.
10. Hannan TJ, Totsika M, Mansfield KJ, et al. Host-pathogen checkpoints and population bottlenecks in persistent and intracellular uropathogenic Escherichia coli bladder infection. FEMSMicrobiol Rev 2012;36(3):616–48.
11. Tenke P, Koves B, Nagy K, et al. Update on biofilm infections in the urinary tract. World J Urol 2012;30(1):51–7.
12. Hall CW, Mah TF. Molecular mechanisms of biofilm-based antibiotic resistance and tolerance in pathogenic bacteria. FEMSMicrobiol Rev 2017;41(3):276–301.
13. Bailiff NL, Westropp JL, Nelson RW, et al. Evaluation of urine specific gravity and urine sediment as risk factors for urinary tract infections in cats. Vet ClinPathol 2008;37(3):317–22.
14. Puchot ML, Cook AK, Pohlit C. Subclinical bacteriuria in cats: prevalence, findings on contemporaneous urinalyses and clinical risk factors. J Feline Med Surg 2017;19(12):1238–44.

15. Olby NJ, MacKillop E, Cerda-Gonzalez S, et al. Prevalence of urinary tract infection in dogs after surgery for thoracolumbar intervertebral disc extrusion. J Vet Intern Med 2010;24(5):1106–11.
16. Merkel LK, Lulich J, Polzin D, et al. Clinicopathologic and microbiologic findings associated with emphysematous cystitis in 27 dogs. J Am AnimHosp Assoc 2017;53(6):313–20.
17. Forrester SD, Troy GC, Dalton MN, et al. Retrospective evaluation of urinary tract infection in 42 dogs with hyperadrenocorticism or diabetes mellitus or both. J Vet Intern Med 1999;13(6):557–60.
18. Thornton LA, Burchell RK, Burton SE, et al. The effect of urine concentration and pH on the growth of Escherichia coli in canine urine in vitro. J Vet Intern Med 2018;32(2):752–6.
19. Foster JD, Krishnan H, Cole S. Characterization of subclinical bacteriuria, bacterial cystitis, and pyelonephritis in dogs with chronic kidney disease. J Am Vet Med Assoc 2018;252(10):1257–62.
20. Peterson AL, Torres SM, Rendahl A, et al. Frequency of urinary tract infection in dogs with inflammatory skin disorders treated with ciclosporin alone or in combination with glucocorticoid therapy: a retrospective study. Vet Dermatol 2012; 23(3):201-e43.
21. Lockwood SL, Schick AE, Lewis TP, et al. Investigation of subclinical bacteriuria in cats with dermatological disease receiving long-term glucocorticoids and/or ciclosporin. Vet Dermatol 2018;29(1):25-e12.
22. Burton EN, Cohn LA, Reinero CN, et al. Characterization of the urinary microbiome in healthy dogs. PLoS One 2017;12(5):e0177783.
23. Gronberg-Hernandez J, Sunden F, Connolly J, et al. Genetic control of the variable innate immune response to asymptomatic bacteriuria. PLoS One 2011; 6(11):e28289.
24. Flokas ME, Andreatos N, Alevizakos M, et al. Inappropriate management of asymptomatic patients with positive urine cultures: a systematic review and meta-analysis. OpenForum Infect Dis 2017;4(4):ofx207.
25. Trautner BW. Asymptomatic bacteriuria: when the treatment is worse than the disease. Nat Rev Urol 2011;9(2):85–93.
26. Weese JS, Blondeau JM, Boothe D, et al. Antimicrobial use guidelines for treatment of urinary tract disease in dogs and cats: antimicrobial guidelines working group of the international society for companion animal infectious diseases. Vet Med Int 2011;2011:263768.
27. Wan SY, Hartmann FA, Jooss MK, et al. Prevalence and clinical outcome of subclinical bacteriuria in female dogs. J Am Vet Med Assoc 2014;245(1):106–12.
28. Sorensen TM, Bjornvad CR, Cordoba G, et al. Effects of diagnostic work-up on medical decision-making for canine urinary tract infection: an observational study in Danish small animal practices. J Vet Intern Med 2018;32(2):743–51.
29. Tivapasi MT, Hodges J, Byrne BA, et al. Diagnostic utility and cost-effectiveness of reflex bacterial culture for the detection of urinary tract infection in dogs with low urine specific gravity. Vet ClinPathol 2009;38(3):337–42.
30. Reine NJ, Langston CE. Urinalysis interpretation: how to squeeze out the maximum information from a small sample. Clin Tech SmallAnimPract 2005; 20(1):2–10.
31. Swenson CL, Boisvert AM, Gibbons-Burgener SN, et al. Evaluation of modified Wright-staining of dried urinary sediment as a method for accurate detection of bacteriuria in cats. Vet ClinPathol 2011;40(2):256–64.

32. O'Neil E, Horney B, Burton S, et al. Comparison of wet-mount, Wright-Giemsa and Gram-stained urine sediment for predicting bacteriuria in dogs and cats. Can Vet J 2013;54(11):1061–6.
33. Lund HS, Krontveit RI, Halvorsen I, et al. Evaluation of urinalyses from untreated adult cats with lower urinary tract disease and healthy control cats: predictive abilities and clinical relevance. J Feline Med Surg 2013;15(12):1086–97.
34. Way LI, Sullivan LA, Johnson V, et al. Comparison of routine urinalysis and urine Gram stain for detection of bacteriuria in dogs. J Vet EmergCritCare (San Antonio) 2013;23(1):23–8.
35. Kvitko-White HL, Cook AK, Nabity MB, et al. Evaluation of a catalase-based urine test for the detection of urinary tract infection in dogs and cats. J Vet Intern Med 2013;27(6):1379–84.
36. Jacob ME, Crowell MD, Fauls MB, et al. Diagnostic accuracy of a rapid immunoassay for point of-care detection of urinary tract infection in dogs. Am J Vet Res 2016;77(2):162–6.
37. Daniels J, MN, Byron JK. Evaluation of a rapid immunoassay for point-of-care detection of bacteria in cat urine. ACVIM forum proceedings 2017. Available at: https://www.vin.com/members/cms/project/defaultadv1.aspx?id=8011996&pid=18492&. Accessed August 30, 2018.
38. Ybarra WL, Sykes JE, Wang Y, et al. Performance of a veterinary urine dipstick paddle system for diagnosis and identification of urinary tract infections in dogs and cats. J Am Vet Med Assoc 2014;244(7):814–9.
39. Guardabassi L, Hedberg S, Jessen LR, et al. Optimization and evaluation of Flexicult(R) Vet for detection, identification and antimicrobial susceptibility testing of bacterial uropathogens in small animal veterinary practice. Acta Vet Scand 2015;57:72.
40. Uhl A, Hartmann FA, Viviano KR. Clinical performance of a commercial point-of-care urine culture system for identification of bacteriuria in dogs. J Am Vet Med Assoc 2017;251(8):922–8.
41. Palamara JD, Bonczynski JJ, Berg JM, et al. Perioperative Cefovecin to reduce the incidence of urinary tract infection in dogs undergoing hemilaminectomy. J Am AnimHosp Assoc 2016;52(5):297–304.
42. Raditic DM. Complementary and integrative therapies for lower urinary tract diseases. Vet Clin North Am SmallAnimPract 2015;45(4):857–78.
43. Olby NJ, Vaden SL, Williams K, et al. Effect of cranberry extract on the frequency of Bacteriuria in dogs with acute thoracolumbar disk herniation: a randomized controlled clinical trial. J Vet Intern Med 2017;31(1):60–8.
44. Hutchins RG, Vaden SL, Jacob ME, et al. Vaginal microbiota of spayed dogs with or without recurrent urinary tract infections. J Vet Intern Med 2014;28(2):300–4.
45. Sunden F, Hakansson L, Ljunggren E, et al. Escherichia coli 83972 bacteriuria protects against recurrent lower urinary tract infections in patients with incomplete bladder emptying. J Urol 2010;184(1):179–85.
46. Segev G, Sykes JE, Klumpp DJ, et al. Evaluation of the live biotherapeutic product, asymptomatic bacteriuria Escherichia coli 2-12, in healthy dogs and dogs with clinical recurrent UTI. J Vet Intern Med 2018;32(1):267–73.
47. Thompson MF, Schembri MA, Mills PC, et al. A modified three-dose protocol for colonization of the canine urinary tract with the asymptomatic bacteriuria Escherichia coli strain 83972. Vet Microbiol 2012;158(3–4):446–50.