Diagnosing and Treating Urinary Tract Infection in Cats

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Urinary tract infection (UTI) exists when bacteria colonize portions of the urinary tract that are normally sterile (i.e., kidney, ureter, bladder, proximal urethra). UTI most commonly affects the bladder. Bacterial colonization may be superficial along the mucosa, or deeper within the mucosa or submucosa. Bacterial UTI is far less commonly diagnosed in cats compared to dogs and is estimated to affect 1-3% of cats in their lifetime. Dogs with no identifiable anatomical, metabolic, or urinary functional problems of the urethra or bladder can acquire UTI, which is quite different for UTI that develops in most cats. Cats that develop UTI are by definition considered "complicated" since healthy cats have exquisite urinary tract defense systems that simply do not allow a "casual" development of UTI. Cats with bacterial UTI will most often be discovered to have anatomical, metabolic, or functional problems of the bladder or urethra, or have undergone urinary tract instrumentation (e.g. urinary catheterization) that facilitate bacterial ascent and colonization of the urinary tract.

Diagnosis

Various combinations of hematuria, pyuria, and bacteriuria are observed in urinary sediment from cats with LUT signs associated with a positive quantitative urine culture (clinical UTI). In cats without LUT signs evaluated for other reasons, a positive urine culture in substantial quantity can be documented (occult or asymptomatic UTI – discussed later). The isolation of bacteria in large quantities does not determine whether the UTI is located in the upper or lower urinary tract, if the UTI is chronic or acute, or if the infection is deep within tissue or superficial along the mucosa.

It is important to remember that many particles in urinary sediment from cats, more so than dogs, resemble bacteria – lipid droplets, small crystals, cellular fragments, mucus, stain precipitates. Dry-mount examination of urinary sediment following either Wright's-Giemsa or Gram stain to further identify bacteria in urinary sediment from cats increases the certainty that UTI really exists or it does not.[1] Urinalysis and aerobic quantitative urine culture reported in colony-forming units per milliliter (cfu/mL) should be conducted in all cats suspected of having a UTI. Isolation of organisms in large quantitative growth (cfu/mL) from a properly collected and handled sample is the gold standard for definitive diagnosis. The number of cfu/mL needed to definitively confirm the existence of UTI varies depending on how the urine is collected and whether clinical signs are present. Lower cfu/ml are often considered clinically significant in patients with increased voiding frequency in which organisms may be eliminated from the bladder before they have time to replicate to higher numbers.

Do not submit sterile swabs soaked or dipped in urine since quantitative culture methods cannot be performed on this type of sample. Culture of urine following cystocentesis is the method of choice to most easily establish a definitive diagnosis of UTI as this bypasses potential contamination with organisms from the distal urethra or genital tract.[2,3] Far less contamination with bacterial organisms occurs during collection of voided or catheterized urine samples from cats compared to dogs. In 24 samples from healthy cats of both sexes, no growth occurred when urine was collected by cystocentesis. Minimal cfu/ml of bacterial growth occurred from samples collected by urinary catheter. In 9 of 12 samples from male cats no growth occurred; 3 samples grew between 10 and 100 cfu/ml. No growth occurred in 11 of 12 samples from female cats in samples collected by catheter; in 1 sample between 100 and 1,000 cfu/ml growth occurred. Quantitative growth (cfu/ml) was much greater in both male and female cats from urine samples collected by voiding. Organisms grew from all 11 urine samples collected by voiding from male cats. Quantitative growth ranged from 100 to > 100,000 cfu/ml in these samples; in 6 of 11 samples, growth exceeded 1,000 cfu/ml (> 10,000 cfu/ml in 2 samples). No growth occurred in 5 of 12 samples collected by voiding from female cats; in 4 of 7 positive cultures, growth was 1,000 to 10,000 cfu/ml and in 1 > 100,000 cfu/ml. In samples with positive growth, more than one organism was frequently isolated. *Escherichia coli, Staphylococcus* spp, *Streptococcus* spp, *Corynebacterium* spp, *Pasteurella* spp, and *Flavobacterium* spp were the organisms isolated in decreasing frequency from the urine of these normal cats.[4]

True bacterial UTI is likely in cats when ≥ 1,000 cfu/ml of organisms are isolated from urine collected by cystocentesis; < 1,000 cfu/ml is more likely to be from contamination during the collection process. Low-level growth from cystocentesis samples is possible in cats with true UTI when antibacterial treatment has been given recently. UTI is likely to exist when ≥ 1,000 cfu/ml are isolated from urine collected by urinary catheterization from either male or female cats; < 1,000 cfu/ml is most likely associated with contamination. Some criteria state that UTI is likely in cats isolating ≥ 10,000 cfu/ml from voided urine[5], but this may not always be true since high level contamination occasionally occurs in both male and female cats using this method of collection.[4] Culture of voided urine is not recommended since high level growth can occur from contamination rather than indicating true UTI, though no growth on voided urine samples does provide meaningful information.

The Uricult® Vet dip paddle system (LifeSign, Skillman, NJ) can be a useful in-house screening tool for identification of bacterial growth.[6] Quantitative results (cfu/mL) determined by comparing growth on the paddles with a standard illustration of organism

density provided by the manufacturer were not always accurate. Inaccuracy in identification of isolated organisms sometimes occurred when paddles were used, particularly when multiple uropathogens were present. This paddle system provides no method for susceptibility testing of isolated organisms, although the bacteria can be categorized into gram-positive or gram-negative status. When growth occurs, paddles or a fresh urine sample should be submitted to a commercial microbiology laboratory for identification and antimicrobial susceptibility testing. Veterinary hospitals should determine whether their referral microbiology laboratory will accept organisms already growing on paddles for definitive identification and minimum inhibitory concentration (MIC) testing. This paddle system for organism isolation appears most clinically useful as an in-house method to identify urine samples that are sterile or samples with low quantitative growth compatible with contamination during the sample collection.[6]

The Accutest Uriscreen® is an in-house color reaction based test designed to rapidly detect catalase from bacteria and from cells in the urine sample from dogs and cats. A negative test supports that UTI does not exist but there are false positives for UTI, so a positive test necessitates a follow-up quantitative urine culture.[7]

Organisms isolated from cats with UTI

Twenty-five percent of urine cultures from cats not biased toward those diagnosed with urinary disease were positive for bacterial growth considered indicative of a UTI in one report from a teaching hospital. The criteria to establish a UTI included any growth in a cystocentesis sample, $\geq$ 1,000 cfu/ml in catheterized samples, and $\geq$ 10,000 cfu/ml in voided urine. The number of cats with true UTI is likely overestimated in this study due to the entry criteria. Eighteen bacterial species were isolated in this study. *E. coli* accounted for 47% of the isolates, *Staphyolococcus* spp for 18%, and *Streptococcus* spp for 13%. A single bacterial isolate occurred in 85%; > 1 isolate occurred in 15% of the positive cultures. The USG of cats infected with E. coli tended to be < 1.025 whereas those infected with Staph or Strep were usually > 1.025. Older female cats were over represented, as were Siamese cats.[8] *E.coli* and gram positive cocci were also the most commonly isolated organisms from Australian cats with UTI in other reports. Older female cats were also more likely to have a positive urine culture as in the previously mentioned study. *E. coli* was isolated in 37% of the positive cultures, *Enterococcus* species in 29%, *Staphylococcus felis* in 20% and *Proteus* species in 5%. *Enterococcus fecalis* accounted for 95% of enterococci spp with the remainder by *enterococcus faecium*.[9,10] *Enterocccus* accounted for 19% of positive urine culture from cats evaluated at the OSU CVM.[11] *Staphylococcus felis* is a coagulase-negative organism that has traditionally been considered a normal commensal organism from healthy cats present on the skin, eyelid margins, conjunctival sac, and in saliva, but appears that this organism can be a uropathogen for the cat.[9]

Occult UTI was documented in 38 of 132 urine specimens (44 isolates) collected by cystocentesis from cats without LUT signs, inappropriate urination, or previous UTI – these samples were submitted as part of other diagnostic workups for a variety of conditions including CKD, hypethyroidism, and diabetes mellitus. Hematuria and pyuria were common in the urinalyses from urine culture-positive cats and culture-positive urine specimens were more likely to come from older female cats. *Enterococcus faecalis* was the most common isolate (19 of 44 total isolates) followed by E. coli (17 of 44 isolates). A few isolates of *Proteus mirabilis*, *Staphylococcus felis*, and *Streptococcus bovis* were also documented in this group of cats. Heavy growth of bacteria at $\geq$ 100,000 cfu/mL was documented in 39 of 44 isolates and moderate growth at 10,000 to 100,000 cfu/mL was found in 5 of 44 isolates.[12] Occult bacteriuria that is either persistent or transient has been described in apparently healthy dogs or those presented for elective surgical procedures[13,14] but this has not been reported in healthy cats. Urine was collected by cystocentesis from 108 healthy cats (53 males and 55 females) with a median age of 4.0 years without previous or current LUT signs. Both urine and urine sediment underwent quantitative culture resulting in no growth in 107 of 108 samples. In the remaining sample >100,000 cfu/mL of 2 organisms was isolated, likely the result of contamination.[15]

A unique form of relapsing UTI is caused by *Corynebacterium urealyticum*[16,17] or *corynebacterium jeikeium*[18] in which encrustations of urinary tissue and struvite (so-called "encrusting cystitis") prevent eradication of the organism with medical treatment alone. These organisms are rarely isolated as a cause for UTI in cats but may be under-diagnosed. These organisms are often reported as "dipitheroids" thought to be contaminants that are not further characterized. These organisms are often slow growing and require special media to facilitate their growth and identification. These organisms are highly resistant to commonly prescribed urinary antibacterials and the prognosis for cure is generally poor even with surgery and long-term antibiotics.

Conditions associated with UTI in cats

UTI occurs with increased frequency in special populations of cats that include those with metabolic disease (CKD, hyperthyroidism, diabetes mellitus), prior instrumentation of the urinary tract with urinary catheterization, urinary incontinence, acquired anatomical abnormalities (stones, tumors, perineal urethrostomy), and congenital anomalies. Chronic kidney disease (CKD), hyperthyroidism, and/or diabetes mellitus all increase the risk for cats to acquire a true bacterial UTI,[19] though clinical signs of UTI may not be present (asymptomatic bacteriuria). In one study 10–15% of cats with hyperthyroidism, diabetes mellitus or chronic renal disease had a bacterial UTI,[12] similar to findings of other studies.[19-21]

In a report comparing 155 cats with UTI to 186 cats without UTI, significant risk factors to acquire UTI were identified for cats with urinary incontinence, transurethral procedures, gastrointestinal diseases, decreased body weight, and decreased urine specific gravity. In this study, 35.5% of cats had no clinical signs associated with their UTI (asymptomatic bacteriuria). UTI in this study was defined as any growth from samples collected by cystocentesis and $> 10^3$ cfu/mL from samples collected by urethral catheterization[22]. Decreased urinary specific gravity was not identified as a risk for UTI in cats of another study.[19]

An early report drew attention to the apparently high rate of UTI in cats with azotemic CKD. Five of 15 CKD cat urine samples without obvious bacteriuria in urinary sediment grew organisms and 12 of 19 CKD cats with bacteriuria grew organisms. Whether or not these CKD cats had LUT signs associated with a positive urine culture was not addressed.[23] The finding of a positive urine culture in cats with CKD could be associated with infection within the kidneys but often this cannot be proven to exist. In a study of 42 female and 44 male cats with CKD undergoing routine urine culture surveillance, positive urine cultures in samples collected by cystocentesis were identified 31 times from 25 cats over a period up to 3 year of their CKD. Eighteen of the 25 cats (72%) were classified as having occult UTI. Eighty-seven percent of cats with positive urine cultures were found to have active urinary sediment. Increasing age was a significant risk factor to acquire occult UTI in female CKD cats. The presence of UTI was not associated with the severity of azotemia or survival in these cats[24].

The frequency of UTI in reports of young cats with non-obstructive LUT signs is quite low (often reported at less than 2%) in most studies in North America, the UK and Europe. [25-31]. Idiopathic/interstitial cystitis accounts for 60 to 70% of diagnoses in cats presenting for some form of urinary urgency. In cats older than 10 years, UTI appeared to be quite common (>50%) in those evaluated for signs of urinary urgency; idiopathic cystitis accounted for only 5% of cases in this group of cats.[32,33]

A study in 2007 of cats from Norway with a variety of obstructive and non-obstructive causes of LUT signs[34] found a surprisingly high number of cats with positive urine culture in large quantitative growth, far more so than in other reports. Findings from this study are difficult to interpret since many of the cultures were from voided midstream (46%) or catheterized urine samples (21%) rather than from the gold standard of cystocentesis (21%); in 10% the method of urine collection was not recorded. 44 of 118 samples cultured on the same day isolated bacteria $> 10^3$ cfu/ml. In 33 of these 44 samples, growth was $> 10^4$ cfu/ml and in 20 growth was $> 10^5$ cfu/ml. Quantitative growth from midstream voided samples from healthy cats is sometimes substantial as was shown in 55% of males and 40% of females that grew $> 10^3$ cfu/ml in another study [4].

Congenital anomalies of the urinary tract are occasionally the cause of UTI in young cats. Any condition associated with non-urge related incontinence can be expected to be associated with UTI. A common urogenital sinus malformation was found as the underlying cause for UTI and incontinence in 3 young female cats that were evaluated for recurrent lower urinary tract infections and incontinence (Ohio State University CVM 2014 – publication in preparation). Fusion of the vagina to the proximal urethra created a single vaginourethra. No vestibule existed as the vulva and urethra appeared as a continuous structure that allowed easy fecal contamination. Cystoscopy was the diagnostic tool used in these cases to confirm the abnormal anatomical status. Partial invagination of the urinary bladder was diagnosed in one cat with clinical signs of hematuria, stranguria, and inappropriate urination associated with UTI. This diagnosis may be made on the basis of detection of invaginated tissue in the bladder apex during abdominal ultrasonography.[35]

Treatment

Antibacterial susceptibility testing on isolated organisms is recommended to guide the best treatment selection. Results can reveal the presence of resistance organisms that can predict treatment failure and the need for greater surveillance following treatment. A change in urinary antimicrobial may be needed based on the results of susceptibility testing after the initial treatment was started at the time of submission of the culture.

The Working Group of the International Society for Companion Animal Infectious Diseases (ISCAID) recommends treatment with urinary antibacterial drugs that are likely to be effective against more than 90% of the urinary isolates when this information is available. In general, ISCAID recommends initial therapy for uncomplicated UTI with amoxicillin (11–15 mg/kg PO q8h) or trimethoprim–sulfonamide (TMP-sulfa; 15 mg/kg PO q12h); the group does not recommend amoxicillin–clavulanate for initial treatment in these cases because of lack of evidence for the need for clavulanate in addition to amoxicillin.[36] Additional detail and a free PDF download of this work published by Veterinary Medicine International is available at http://www.hindawi.com/journals/vmi/2011/263768/.

Amoxicillin/clavulanic acid was recommended for Gram-negative infections and amoxicillin for Gram-positive infections in one review of cats with UTI. Variation in bacterial prevalence and susceptibility patterns should also be taken into account when prescribing antibacterial treatment[10] Most isolates of *E.coli* in one study showed susceptibility to the 14 antimicrobials tested. *Staphylococcus* felis was susceptible to all antimicrobial agents tested. Enterococcus was universally sensitive to amoxicillin/clavulante and penicillin/amoxicillin in 2 studies of UTI in cats by the same group.[9,12] *Enterococcus faecalis* can vary greatly in its susceptibility pattern to antimicrobial agents and so may require higher dosage, longer duration or a combination of therapeutic agents in some patients with overt LUT signs. A high proportion of *Enterococcus* isolates were resistant to clindamycin

(97.3%) and cephalothin (72.3%). *Enterococcus* had intermediate susceptibility to enrofloxacin, (61.1%) and marbofloxacin (80.5%).[9] All cephalosporins, potentiated sulfas, and aminoglycosides are notoriously ineffective against *Enterococcus* even when the susceptibility test results return as sensitive for those drugs. *Enterococcus* is usually susceptible to imipenem and meropenem BUT use of these drugs should be restricted to those cases that have LUT signs and have failed treatment with amoxicillin or amoxicillin-clavulante. Current recommendations are to NOT treat asymptomatic UTI associated with *enterococcus* since this infection can come and go without treatment. Aggressive treatment for asymptomatic UTI runs the risk that the original *enterococcus* will become more resistant and then become symptomatic when it was not before. There is also the possibility that the *enterococcus* will be eradicated, but UTI with a more virulent and symptomatic organism will take its place.

Resistance patterns were reported for isolates of *E. coli* mostly from urine of dogs (301)and cats (75) in various regions of the United States. Resistance to amoxicillin was 46%, amoxicillin-clavulanate 37%, cefpodoxime 22%, doxycycline 22%, enrofloxacin 21%, trimethoprim-sufla 19%, and gentamicin at 12%. This pattern for E. coli resistance suggests that empirical treatment for UTI may have limited success in this geographic location. Treatment of *E. coli* with amoxicillin or with amoxicillin-clavulanate may be less likely to be effective than commonly believed.[37]

An early report documented the effectiveness of enrofloxacin treatment of UTI in cats. In this study all isolates were considered susceptible to enrofloxacin and post treatment sterility was documented in 21 of 23 cats.[38] As noted above, there are concerns for increasing resistance patterns for *E. coli* in the United States; there are no recent reports of UTI in cats treated with enrofloxacin. The total daily dose of enrofloxacin in cats should be limited to 5 mg/kg either once daily, or divided in order to limit retinal toxicity. Retinal toxicity is a fluroquinolone class risk, especially for those that achieve the highest retinal concentrations and can result in mydriasis and blindness.[39,40] It appears that cats as a species have developed a limited efflux mechanism to remove fluoroquinolones from the retina compared to other species.[41] High-dose short-duration protocols prescribing enrofloxacin to treat UTI have been developed for use in dogs with uncomplicated UTI[42] but these protocols should NEVER be used in cats due to retinotoxicity that predictably develops at high doses. Administration of the 3rd generationi fluroquinolone pradofloxacin at 6 to 10 times the recommended dose was shown to have no retinal toxic effects in cats based on rod and cone function evaluated with ERG. Retinal histopathology was unaltered during high dose pradofloxacin treatment. Cats treated with high doses of enrofloxacin showed diffuse retinal degeneration and poor rod and cone function.[40]

Cefovecin is an extended spectrum semi-synthetic 3rd generation cephalosporin approved in Europe for use in cats with UTI caused by *E. coli*, but not approved for this indication in the United States. It is designed to have a 14-day dosing interval after a single subcutaneous injection. Post treatment urine cultures revealed sterile urine in 75.9% of all cats treated with a single injection of cefovencin. *Escherichia coli* was eliminated in 76.7 per cent of cefovecin-treated cats compared with 62.5 per cent of cephalexin-treated cats. Cefovecin demonstrated statistical non-inferiority compared with cephalexin for bacterial

elimination in this study. [43] Efficacy of cefovecin to sterilize the urine in cats with UTI was less than that reported by the same group in dogs with UTI.[44]

Client-owned cats with bacteriologically confirmed UTI were treated with either pradofloxacin, doxycycline, or amoxicillin-clavulante[45] Urine culture revealed growth following treatment in 0 of 27 cats treated with pradofloxacin, 3 of 23 cats treated with doxycycline, and in 3 of 28 cats treated with amoxicillin-clavulante.[45] Pradofloxacin undergoes more hepatic excretion than does enrofloxacin but still achieves urinary concentrations that can be highly effective in the eradication of uropathogens. Pradofloxacin may be the preferred fluoroquinolone to prescribe for use in cats with UTI and impaired renal function due to the hepatic pathway for its excretion and its retinal safety profile should high concentrations of pradofloxacin accumulate in cats with decreased renal function. Pradofloxacin is FDA approved for soft tissue infections in cats; it can be considered for off-label treatment of UTI in cats.

Study of canine and feline *E.coli* isolates that were considered highly resistant to standard antimicrobial agents showed susceptibility to fosfomycin at concentrations well below the susceptible breakpoint. This finding makes it attractive to consider fosfomycin as a treatment for resistant *E. coli*.[46] Fosfomycin is considered a nephroprotectant in some species but in cats this drug can be highly nephrotoxic. When given to experimental cats for as little as 3 days, severe tubular lesions were evident and renal function declilned as BUN and serum creatinine increased.[47]

The recommendation of 7 to 14 days of an appropriate antimicrobial for treatment of an uncomplicated lower UTI has been based on conventional experience over the years, but surprisingly little data exist to support or refute these protocols. Ultimately, antimicrobials should be given for as long as is necessary to effect a bacteriologically sterile urine during administration of the medication and for a protracted time following discontinuation of treatment.

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