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Review

Feline bacterial urinary tract infections: An update on an evolving clinical problem

Annette Litster [a,*], Mary Thompson [b], Susan Moss [b], Darren Trott [b]

[a] Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Purdue University, 625 Harrison St., West Lafayette, IN 47907, USA
[b] School of Veterinary Science, University of Queensland, St. Lucia, Queensland 4072, Australia

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ABSTRACT

Although feline urine is increasingly submitted for bacterial culture and susceptibility testing as part of a more general diagnostic work-up for a range of presentations in veterinary practice, bacterial urinary tract infections (UTIs) are relatively uncommon due to a variety of physical and immunological barriers to infection. Culture positive urine is most often obtained from older female cats and the clinical history may include hematuria, dysuria and pollakiuria, or the infection may be occult. Urinalysis usually reveals hematuria and pyuria, and *Escherichia coli* and Gram-positive cocci are cultured most frequently. Most feline UTIs can be successfully treated using oral amoxicillin or amoxicillin/clavulanic acid administered for at least 14 days, but the prevalence of antimicrobial resistance amongst infecting bacterial species is a growing concern. There is currently no conclusive information on the safety and efficacy of alternative therapeutic agents for the treatment of feline UTIs.

Introduction

Although clinical signs of lower urinary tract disease (such as dysuria, stranguria, pollakiuria, hematuria) are common in feline practice (Buffington et al., 2006), bacterial urinary tract infections (UTIs) in cats are relatively rare (Bartges and Barsanti, 2000). The reported prevalence is variable, depending on the inclusion criteria of investigating studies. Studies of cats with clinical signs of lower urinary tract disease (dysuria, stranguria, pollakiuria) have consistently shown that the overall prevalence of positive bacterial urine cultures is <3% (Kruger et al., 1991; Buffington et al., 1997). Some studies have reported much higher prevalence rates (15–43%) in cats that have their urinary tract defence mechanisms compromised by the effects of other diseases and/or by the treatment (e.g., urinary catheterization, perineal urethrostomy) (Mayer-Roenne et al., 2007).

In one experimental study in which perineal urethrostomy was performed in healthy castrated cats and cats with recurrent or persistent urethral obstruction, 22% of the previously obstructed cats developed recurrent bacterial UTIs, but UTIs did not occur in the other group, leading the authors to conclude that underlying uropathy was necessary in urethrostomized cats for bacterial UTIs to occur (Griffin and Gregory, 1992). In a study by Kraijer et al. (2003), 8/36 (22%) cats with clinical signs of lower urinary tract disease, but no apparent predisposing factors, had positive bacterial urine culture results.

In this review, we discuss the interaction between the host and the bacterial uropathogens from a clinical perspective, examining the delicate balance between the host immune response and the mechanisms used by bacteria to circumvent these defences. Risk factors for bacterial UTIs are reviewed, emphasizing information obtained from urinalysis, as well as clinical presentations and reported bacterial isolates. Finally, antimicrobial therapies are described, including recent information on the development of antimicrobial resistance and its impact on recommendations for successful treatment of feline UTIs.

Host defence mechanisms in the feline urinary tract

The lower urinary tract has a variety of host defence mechanisms to prevent bacterial UTIs. Physical barriers such as the length of the urethra, high pressure zones within the urethra, bacteria-trapping longitudinal folds in the proximal urethra, and urethral peristalsis resulting in a unidirectional urine flow, form the first line of defence. These are supported by mucosal defence barriers, including a glycosaminoglycan layer and intrinsic mucosal antimicrobial properties, to prevent bacterial migration and colonization, and by the composition of the urine (Blanco and Bartges, 2001; Bartges, 2005).

Normal cat urine is highly concentrated, with urine specific gravity often exceeding 1.045 and with an associated high osmolality (Lees and Rogers, 1986). High concentrations of urea and organic acids and secreted antimicrobial peptides that inhibit bacterial colonization work together with the acquired cell-mediated and antibody-mediated immune response (Blanco and Bartges, 2001;

* Corresponding author. Tel.: +1 765 418 3186; fax: +1 765 496 1108.
E-mail address: catvet@purdue.edu (A. Litster).

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Bartges, 2005), making the feline urinary tract a remarkably hostile environment for bacterial growth compared to that of other species. It is not surprising therefore that bacterial UTIs in cats are relatively rare events (Bartges and Barsanti, 2000).

Bacterial pathogens of the feline urinary tract

Bacterial uropathogens in cats are similar to those reported for dogs, with *Escherichia coli* and *Streptococcus/Enterococcus* species accounting for most UTIs in both species (Bartges and Barsanti, 2000). In a recent study of 107 cats with symptomatic UTIs, the majority of Gram-negative bacterial isolates were also *E. coli*, while the most common Gram-positive bacterial isolate was *E. faecalis* (Table 1; Litster et al., 2007a). The rapid urea-splitting, intrinsically tetracycline resistant *Proteus* species was the second most common Gram-negative bacillus involved in feline UTIs (Litster et al., 2007a).

In this study, *Staphylococcus felis*, a previously unrecognized feline urinary tract pathogen, was the third most common isolate (Litster et al., 2007a). For this coagulase-negative staphylococcus, the current commercial phenotypic identification systems could not differentiate between *S. felis* and the other coagulase-negative staphylococcal species, in particular *S. simulans*. This necessitated the use of partial 16S rDNA sequencing, which identified all the coagulase-negative isolates as *S. felis* (Litster et al., 2007a). *S. felis* was first recognized from feline clinical specimens in 1989 (Igimi et al., 1989) and is regarded as a normal commensal organism present on the skin (Lilenbaum et al., 1998), the conjunctival sac and eyelid margins (Espinola and Lilenbaum, 1996) and in the saliva (Lilenbaum et al., 1999). In the study of Litster et al. (2007a), all *S. felis*-positive specimens were obtained aseptically by cystocentesis from cats with clinical signs of lower urinary tract disease, thereby minimizing the possibility of sample contamination by commensal organisms from the skin or lower urethra. The high prevalence of *S. felis*-positive UTIs reported (19.8% of bacterial isolates cultured) suggests that this organism is a common urinary tract pathogen of cats.

There have recently been case reports of *Corynebacterium urealyticum* (previously known as *Corynebacterium* group D2) in association with lower UTIs in cats (Bailiff et al., 2005; Cavana et al., 2008). These non-hemolytic Gram-positive, rapid urea-splitting bacilli are uncommon causes of UTIs in dogs and they present diagnostic and therapeutic challenges because of slow in vitro growth and the multidrug resistant nature of the pathogen (Bailiff et al., 2005). Risk factors for this type of infection include urological procedures, foreign bodies, bladder mucosa abnormalities, immunosuppressed states and antibiotic treatment (Cavana et al., 2008). In particular, because of the ability of this organism to hydrolyze urea, infection may be associated with encrusting cystitis, a condition causing precipitation of struvite or calcium phosphate plaques on the bladder mucosa. Treatment should be based on the results of the most recent antimicrobial susceptibility patterns available and treatment of any predisposing factors (Bailiff et al., 2005).

Bacterial virulence mechanisms

UTI culminates from the expression of bacterial virulence genes responsible for colonization (e.g. flagella, adhesins and iron scavenging systems), avoidance of innate host defences (e.g. capsule) and initiation of host tissue damage (e.g. toxins and invasins). In addition, several urinary pathogens (*Proteus* spp., *C. urealyticum*) possess high urease activity. The resultant cleavage of urea to ammonia is not only irritating to bladder epithelial cells, but increases urinary pH and promotes crystalluria.

Table 1
Bacterial isolates ($n = 126$) from 107 cats with lower urinary tract infections (Litster et al., 2007a).

Bacterial isolate	Total
E. coli	47
Enterococcus species[a]	36
Staphylococcus felis	25
Proteus species[b]	6
Enterobacter/Klebsiella species[c]	4
Pseudomonas aeruginosa	2
Staphylococcus aureus	2
Staphylococcus intermedius	2
Streptococcus bovis	2
Total number of isolates	126

[a] *Enterococcus faecalis* ($n = 34$) and *Enterococcus faecium* ($n = 2$).
[b] *Proteus mirabilis* ($n = 5$) and one isolate identified as *Proteus vulgaris*.
[c] One isolate identified as *Enterobacter aerogenes*, two isolates identified as *Enterobacter cloacae* and one *Klebsiella pneumoniae subspecies oxytoca* isolate.

As the most common urinary tract pathogen in both humans and animals, more is known about specific virulence mechanisms in *E. coli* than for any other organism and over 35 specific *E. coli* virulence genes associated with extra-intestinal infection have been identified (Chapman et al., 2006). *E. coli* strains are classified into four phylogenetic groups (A, B1, B2 and D), with virulent extra-intestinal pathogenic *E. coli* (ExPEC) strains, including those isolated from cases of urinary tract infection, mainly confined to group B2 (which typically contain a greater array of virulence genes) and to a lesser extent to group D (Clermont et al., 2000). Most commensal strains belong to groups A or B1 and contain few virulence genes, but these can still be isolated from cases of UTI, particularly in patients with impaired urinary defence mechanisms (Picard et al., 1999). ExPEC strains causing UTIs in humans and dogs share phylogenetic and pathotypic similarity and often express several adhesins (P, S, F1C and type 1 fimbriae) that mediate specific binding to the uroepithelium with different receptor specificities as well as other typical ExPEC virulence factors such as siderophores, capsular factors, cytotoxins and invasins (Sidjabat et al., 2009). However, it is still unclear which subset of virulence genes actually contributes to UTIs, as among the various typically assayed virulence genes, only those encoding type 1 fimbriae are consistently present in uropathogenic strains.

E. coli is the most common bacterial pathogen isolated from cases of urinary tract infection in cats (Litster et al., 2007a), and it appears that feline UTI isolates also possess the typical ExPEC virulence genes and share phylogenetic and pathotypic similarities to human and canine ExPEC (Freitag et al., 2008). Interestingly, in a study of cats with asymptomatic bacteruria, over 80% of the *E. coli* isolates belonged to the more pathogenic phylogenetic group B2 (Litster et al., 2009), and it may be that simple survival in the harsh environment of the feline urinary tract requires many of the virulence factors associated with highly pathogenic strains.

Risk factors: signalment and urinalysis results

Numerous studies have shown that risk factors such as age ($\geqslant$10 years), urinary catheterization and perineal urethrostomy can increase UTI rate markedly (Gregory and Vasseur, 1983; Lekcharoensuk et al., 2001). A recent study of asymptomatic cats reported that culture positive urine specimens were more likely to be obtained from older females (Litster et al., 2009), confirming the results of a previous large epidemiologic study of symptomatic cats (Lekcharoensuk et al., 2001). This finding is also echoed in studies of asymptomatic bacteriuria in humans (Nicolle, 2006) and occult canine UTIs (McGuire et al., 2002). In females of all ages, this is not surprising given the relative ease with which resident

gastrointestinal flora can ascend the relatively short and wide urethra from the perineum and establish an infection.

Microscopic examination of urine sediment is an excellent in-house screening method for identifying UTIs. The presence of an active urine sediment (increased erythrocytes and leukocytes) and the observation of bacteria following a Gram stain are discriminating factors and are important criteria for deciding if bacterial culture is warranted (Bailiff et al., 2008). One recent study reported that the severity of these factors, especially pyuria, on urine sediment examination was strongly correlated with positive urine culture outcome (Bailiff et al., 2008). Interestingly, a recent study, which examined whether decreasing urine specific gravity was associated with positive urine culture, demonstrated that no such association existed (Bailiff et al., 2008), but other studies have reported significantly lower urine specific gravity in Gram-negative UTIs (Litster et al., 2009).

Clinical presentation and the significance of asymptomatic bacteriuria

Feline bacterial UTIs are usually associated with hematuria, pollakiuria, dysuria, stranguria and inappropriate urination, but bacterial UTIs in cats may also be clinically inapparent. Since urine bacterial culture status is becoming part of a minimum database of laboratory information collected for a wide variety of clinical presentations, clinically occult UTIs are increasingly diagnosed. A recent study specifically examined bacterial lower UTIs in cats in the absence of lower urinary tract clinical signs, a history of inappropriate urination, or previous UTIs (including pyelonephritis) (Litster et al., 2009). Only urine specimens that were collected by cystocentesis and yielded moderate or heavy growth on bacterial culture were included, so that iatrogenic bacterial contamination was not a confounding factor. All of the specimens met the widely used interpretive criteria (Osborne and Stevens, 1999) for significant bacteriuria in feline urine ($\geqslant$1000 CFU/mL of bacteria grown from a quantitative culture of urine collected by cystocentesis).

Asymptomatic bacteriuria is a common but usually benign finding in women, and risk factors include pregnancy, diabetes mellitus, spinal cord injury, indwelling urinary catheterization, and being an elderly resident of a nursing home (Nicolle, 2006). Occult bacterial UTIs have also been reported in diabetic dogs, but urinalysis results could reliably predict urine culture status and the presence of bacteriuria was inconsistent (McGuire et al., 2002). In the study of Litster et al. (2009), approximately 10–15% of cats that presented for hyperthyroidism, diabetes mellitus or chronic renal disease had a bacterial lower UTIs, confirming the findings of other studies (Mayer-Roenne et al., 2007; Bailiff et al., 2008). Also, some completely asymptomatic cats presented for routine geriatric checkups had culture positive urine. The positive relationship between age and positive urine culture status reported in the study of Litster et al. (2009) and another study (Lekcharoensuk et al., 2001) may, at least in part, explain this finding.

The bacteria cultured from urine specimens in asymptomatic cats also appeared to have initiated a local inflammatory response, as positive cultures were accompanied by high urine erythrocyte and leukocyte counts (Litster et al., 2009). Asymptomatic bacteriuria in humans is also usually accompanied by pyuria (Nicolle, 2006).

While healthy women identified with asymptomatic bacteriuria subsequently experience more frequent episodes of symptomatic infection, antimicrobial treatment of asymptomatic bacteriuria does not decrease the occurrence of these episodes (Nicolle, 2006). Clinical trials have consistently found no benefits with antimicrobial treatment of human asymptomatic bacteriuria and negative outcomes can occur, such as adverse drug effects and reinfection with organisms of increasing antimicrobial resistance (Nicolle, 2006). Prospective clinical trials comparing clinical outcomes in cats with occult UTIs treated with antimicrobials with an untreated control group would be necessary to decide the optimal management recommendations for these cats.

Antimicrobial treatment of feline bacterial UTIs

E. coli and *Enterococcus* are the most commonly reported pathogens causing feline bacterial UTIs (Bartges and Barsanti, 2000; Litster et al., 2007a, 2009; Gottlieb et al., 2008). In studies by Litster et al. (2007a, 2009), the *E. coli* isolates were sensitive to the majority of the antimicrobials tested, whereas the *Enterococcus* isolates were uniformly sensitive to amoxicillin/clavulanic acid and penicillin/ampicillin and mostly resistant to cephalothin and clindamycin. Based on these findings, in a clinical situation, if high numbers of bacteria are visualized on microscopic examination of a cystocentesis-obtained urine specimen from a cat with or without lower urinary tract signs, and immediate antimicrobial treatment is chosen, prescription of amoxicillin/clavulanic acid for Gram-negative infections and amoxicillin for Gram-positive infections seems reasonable.

Of course, regional variations in bacterial prevalence, bacterial sensitivity patterns and registered drug availability and palatability could affect this recommendation and quantitative urine culture and antimicrobial susceptibility testing is still the recommended 'gold standard' to confirm a bacterial UTI and to determine the appropriate antimicrobial treatment. This is particularly the case with complicated or recurrent UTIs, whereas it seems reasonable to attempt antimicrobial treatment without urine culture in first time acute cases. The majority of *S. felis* isolates were susceptible to all antimicrobials tested, with only two strains resistant to penicillin/ampicillin and only one strain resistant to tetracycline, erythromycin, clindamycin and penicillin/ampicillin.

Pradofloxacin is an 8-cyano-fluoroquinolone developed to treat bacterial infections in dogs and cats (Körber et al., 2002). Molecular substitutions at positions C-7 and C-8 have greatly enhanced the bactericidal activity of pradofloxacin compared to earlier fluoroquinolones, especially for pathogens with reduced fluoroquinolone susceptibility, as its molecular structure restricts bacterial selection for antimicrobial resistance. Pradofloxacin has been shown in vitro to be highly active against a range of canine and feline urinary tract pathogens, including *E. coli* and *Staphylococcus* spp. (Körber et al., 2002). In a recent controlled clinical trial, pradofloxacin 2.5% oral suspension was compared to two other commonly prescribed antimicrobials (doxycycline and amoxicillin/clavulanic acid) for the treatment of feline bacterial lower UTI (Litster et al., 2007b). The post-treatment urine specimen in all cats in the pradofloxacin group ($n = 27$) was negative for bacteria on urine culture. In each of the other two treatment groups (doxycycline, $n = 23$; amoxicillin/clavulanic acid, $n = 28$), there were three cats (doxycycline, 13.0%; amoxicillin/clavulanic acid, 10.7%) in which the post-treatment urine specimen was positive for bacteria on urine culture. However, the difference in proportions of treatment failure among groups was not statistically significant ($P > 0.05$).

Adverse events that were attributed to drug exposure by the attending veterinarian were not reported in the pradofloxacin or doxycycline groups. Three cats initially allocated to the amoxicillin/clavulanic acid treatment group developed gastrointestinal signs that were attributed by the attending veterinarian to drug exposure, resulting in their exclusion from the trial. None of the cats in the pradofloxacin group had pupillary light reflex test abnormalities during therapy (Litster et al., 2007b), which agrees with a recently published experimental study which reported that pradofloxacin at 6 and 10 times the recommended doses had no retinal toxic effects in cats (Messias et al., 2008).

There is an emerging need for palatable oral pharmaceutical formulations for companion animals, and this factor has a major impact on issues such as owner convenience and compliance, particularly for chronically administered medications (Thombre, 2004). The clinical trial reported by Litster et al. (2007b) also assessed the ease of administration by owners of each of the three antimicrobials used, all of which were presented in palatable liquid form. All three antimicrobials tested performed equally well, and none of the participating owners reported inability to medicate their cat during the trial. Owners' perceptions of the difficulty of administering oral medication to their cats were more positive post-treatment than pre-treatment ($P = 0.001$).

Cefovecin, a new extended spectrum semi-synthetic cephalosporin, has a 14-day dosing interval after a single subcutaneous injection and combines rapid absorption with slow elimination due to the protein bound fraction of the drug acting as a reservoir with slow release of free (unbound) drug (Stegemann et al., 2006a). Concentrations of cefovecin in urine collected from cats with normal renal function are maintained above the MIC_{90} of *E. coli* for at least 10 days (Stegemann et al., 2006a). A recent in vitro study reported that cefovecin exhibited activity against all major aerobic and anaerobic bacterial pathogens associated with skin, urinary tract, and periodontal infections in dogs and cats (Stegemann et al., 2006b). Subsequently, a multicenter, masked, randomized study was performed to compare the efficacy and safety of cefovecin with cephalexin for the treatment of feline bacterial UTIs (Passmore et al., 2008). Post-treatment urine cultures revealed that cefovecin eliminated 75.9% of all pathogens (41/54); 76.7% of single and mixed infections with *E. coli* (23/30); and 72.7% of single infections with *E. coli* (16/22) – a lower efficacy than that reported for cefovecin in canine UTIs (Passmore et al., 2007). There were no suspected adverse drug reactions attributable to treatment with cefovecin or cephalexin UTIs (Passmore et al., 2008).

Alternative treatments for persistent or relapsing feline bacterial UTIs

Persistent or relapsing infection as well as re-infection, predominantly with uropathogenic *E. coli*, has been documented in older cats with chronic renal failure (Freitag et al., 2006) and may well occur in other groups of cats with risk factors such as perineal urethrostomy or concurrent medical conditions resulting in altered urine chemistry (Mayer-Roenne et al., 2007). In such cases, repeated courses of antibiotics typically prove ineffective at achieving long-term bladder sterility and a non-antibiotic preventative strategy may be sought.

Strategies trialed in humans to prevent recurrent bacterial UTI include administration of cranberry products containing proanthocyanidins (Jepson and Craig, 2008), D-mannose (Wellens et al., 2008), forskolin (Bishop et al., 2007), methanamine hippurate (Lee et al., 2007, 2009), vitamin A (Yilmaz et al., 2007), nasturtium and horseradish (Albrecht et al., 2007), gastrointestinal probiotics (Lee et al., 2007) and orally administered *E. coli* fractions (Bauer et al., 2002).

Cranberry proanthocyanidins have been shown to inhibit the adherence of *E. coli* to cultured human bladder and vaginal epithelial cells in a linear, dose-dependent fashion (Gupta et al., 2007). In a meta-analysis ($n = 1049$ patients) cranberry products were shown to reduce the incidence of UTIs over a 12-month period compared with a placebo (Jepson and Craig, 2008). Cranberry products were most effective at preventing UTIs in women with recurrent UTIs compared to elderly men and women and did not appear effective in individuals requiring catheterization. The proposed mechanism of action of Heptyl alpha-D-mannose is the blockage of bacterial adhesion via Type 1 fimbriae and this has been demonstrated in cultured human urothelial cells (Wellens et al., 2008). Additionally, this anti-adhesive effectively antagonized adhesion and invasion of mouse bladder cells in vivo.

Sequestration of *E. coli* in urothelial cells is implicated in relapsing cystitis, the bacteria avoiding destruction by antimicrobial agents (Mysorekar and Hultgren, 2006). Forskolin has been recently studied as a strategy for stimulating the efflux of bacteria from urothelial cells via elevation of cAMP levels. Forskolin was proven to reduce the number of intracellular *E. coli* in infected mouse bladder cells in vivo (Bishop et al., 2007). A recent in vitro study of feline uropathogenic *E. coli* (UPEC) showed that most strains studied were susceptible to lysis by naturally occurring bacteriophages, introducing bacteriophages as promising therapeutic agents for treatment of canine and feline *E. coli* UTIs (Freitag et al., 2008). However, it is important to realize that at this time there is no evidence to support the efficacy and safety of alternative therapeutic agents in feline patients with recurrent UTIs and randomized controlled clinical trials are required before they can be recommended for use in clinical practice.

Conclusions

Feline bacterial UTI is mainly a disease of older females or those with predisposing factors impairing their host defences, such as urinary catheterization. It is usually associated with clinical signs such as dysuria, hematuria and pollakiuria, but may be clinically silent. *E. coli* and *Enterococcus* spp. are the most commonly reported bacterial urinary tract pathogens and both are usually sensitive to penicillin analogues or penicillin potentiated with clavulanic acid. Recent studies confirmed that feline urinary tract pathogens are still susceptible to currently registered as well as newly developed antimicrobial agents.

Conflict of interest statement

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