

Recurrent UTI and Current Approaches to Manage Infections

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The development of urinary tract infections (UTIs) is multifactorial, dependent on alterations in anatomical, environmental, and immunological competency. For many individuals with normal urinary defenses bacteria are cleared from the bladder without the need of medical care. Unfortunately, despite the bladder's inherent resistance to bacterial colonization 14% of dogs are estimated to develop UTIs during their lives. Of these cases, the most problematic are recurrent urinary tract infections.

Recurrent infections pose a challenge to the clinician as treatment should be paired with an identification or understanding of the cause of the infection. If the primary reason for bacterial colonization is not identified and addressed the patient may be at risk for developing another UTI. Traditionally, treatment of recurrent infections has relied on characterizing the UTI as a persistent infection or re-infection.

Persistent (Refractory) Infections

Persistent infections occur when appropriate antimicrobial therapy fails to clear the UTI and are typically identified within 2 weeks after completing treatment for the initial infection. Provided that the prescribed antibiotic was administered at the appropriate dose/duration, persistent infections indicate that the infecting bacteria developed resistance, the immune system of the patient is compromised, or the antibiotic is unable to achieve adequate concentrations to eradicate the infection.

Over the last few decades as the incidence of multidrug resistant (MDR) UTI has increased there is a rising population of patients with persistent infections not susceptible to first or even second line antibiotics. These infections can be difficult to manage. Alternative therapies have been proposed that are largely supported by individual case reports and anecdotal evidence. The use of high dose amoxicillin/clavulanic acid is one technique that uses the urine concentrating ability to treat MDR infections that otherwise appear resistant on susceptibility testing. Another approach that has been described to treat resistant organisms is directly instilling aminoglycoside antibiotics into the bladder to attempt sterilization.

Persistent infections can also be caused by inadequate antibiotic tissue concentrations and this can occur for a number of reasons. Decreased intestinal absorption of oral medications, altered perfusion of infected tissue, altered drug metabolism, or reduced urinary concentrating ability all may result in treatment failure. For these reasons, persistent infections require screening for systemic disease including an assessment of the function of the immune, gastrointestinal, hepatic, and renal systems. If the pathology resulting in a persistent infection cannot be corrected then antibiotic doses or route of administration should be adjusted to maximize tissue concentrations or an alternative antibiotic should be chosen.

A subset of persistent infections is termed "relapse". Relapse differs from persistent infection in that during relapse urine can be cleared of infection but bacterial reservoirs remain within the body allowing for urine recolonization with the same organism within a few days to weeks. Sites that may harbor bacterial colonies include the kidneys, prostate, uroliths, vagina, and possibly the urinary bladder wall. The treatment goal for relapsing infections is to identify the site of infection so that eradication of the reservoir infection is ensured. For suspected tissue infections, bacterial sensitivities should be determined based upon the achievable plasma concentrations and tissue penetration of the antibiotic. Therapy is traditionally prolonged with general recommendations of treatment for 4-6 weeks. However the optimal treatment duration to clear these infections is largely unknown. It is possible that in certain circumstances treatment duration could be safely reduced. Relapse due to the formation of intracellular bacterial communities is a unique example of complicated UTI of unknown clinical importance in dogs and cats. In humans and mice small collections of intracellular bacteria can form quiescent intracellular reservoirs that reseed the bladder weeks to months later. Antibiotic therapy even with prolonged treatment duration is unable to clear QIR and currently effective therapy is not known.

Re-infections

Reinfection occurs when there are abnormal host defenses allowing new bacterial strains to colonize the urinary bladder weeks to months after an initial UTI. In both reinfection and relapse a time period exists when the patient's urine is sterile making it challenging to differentiate between the two when similar bacterial species are isolated in subsequent infections. Re-infections require an investigation as to the urinary tract pathology that may be causing the failure in treatment otherwise continued reinfection is likely. This includes a complete systemic evaluation of the patient including advanced diagnostics such as radiographs/contrast studies, ultrasound and cystoscopy. Treatment of reinfection should be paired with urine culture and sensitivity to guide therapy and if clinical signs are mild to absent at the time of UTI diagnosis it is prudent to wait for antibiotic susceptibility results before starting therapy. In instances when treatment must be instituted immediately a first line antibiotic should be chosen. Since reinfection is caused by recolonization with a different bacterial strain each time, treatment duration is similar to the patient having numerous single infections making long antibiotic courses usually unnecessary.

Unfortunately in 25% of dogs the defect allowing re-colonization is not identified resulting in a frustrating cycle of repeat infections and treatment. These repeated infections lead to multidrug resistance and treatment failure. For these reasons a treatment plan focused on prevention of UTI is ideal. Unfortunately, there is little clinical evidence proving the long-term efficacy of nearly all preventative treatments in dogs and cats. Despite this a number of them are used clinically given the lack of alternative options.

UTI Prevention?

Of note: The following therapies are considered UTI preventatives and not treatment. If the patient has a UTI these options should not be used as a sole therapy to clear the infection. Also, nearly all of these options stem from their use in human medicine with variable efficacy and recommendation. In veterinary medicine there is currently a lack of clinical trials proving efficacy of all of these preventatives.

The first group of preventatives is the drugs that work by anti-adherence with cranberry extract and proanthocyanidins (PACs) being one of the most commonly used in dogs and cats. PACs isolated from cranberries can prevent P-fimbriated *E. coli* from binding to urothelial cells. Unfortunately, these molecules do not appear to have a similar effect on many other uropathogenic bacteria (including other *E. coli*) limiting their efficacy. There is data suggesting that the consumption of cranberry juice rather than PACs can block additional bacteria, but the mechanism by which consumption of the juice acts differently than the PACs is not known. The oral administration of D-mannose is a second anti-adherence therapeutic that may block the ability of type 1 fimbriated bacteria to bind to the bladder wall although clinical evidence of efficacy in dogs and cats is lacking. A third anti-adherence preventative is the use of glycosaminoglycans (GAGs). During *E. coli* UTI bacteria can injure the protective GAG barrier overlying the urothelium. GAG therapy contends that exogenous GAG will adhere to the urothelium or bind to invading bacteria preventing bacterial induced injury. In people, numerous independent studies have demonstrated that direct instillation of the GAGs hyaluronic acid and chondroitin sulfate into the urinary bladder significantly reduces UTI recurrence rates. However in veterinary medicine GAG bladder instillations can be challenging and expensive. Current evidence indicates that orally administered GAG may minimally increase urinary GAG concentrations in dogs, but nowhere near the concentration used in intravesicular instillation and so the clinical benefit of orally administered GAG is questionable.

A second group of preventatives are the urinary antiseptics. This group includes methenamine and modified dose antibiotic prophylaxis. Methenamine salts are urinary antiseptics that produce formaldehyde in an acidic urine environment. Since a urine pH of 5.5 is required to convert methenamine to bacteriostatic concentrations of formaldehyde, vitamin C or other urine acidifiers are co-administered to achieve this low pH. In people the long-term benefit of this medication is questionable and is generally only recommended for periods of a week or less. In addition it should be avoided in patients with metabolic acidosis and renal disease. In veterinary medicine there is not evidence supporting its use. In contrast modified dose antibiotic prophylaxis is used in veterinary medicine particularly in some animals suffering from recurrent infections with

severe clinical signs. This treatment will not prevent infection once the antibiotics are discontinued and selective pressures applied to bacteria via repeated courses of antibiotics may lead to the development of multidrug resistant uropathogenic bacterial strains and treatment failure. For that reason, first line antibiotics such as cephalexin, ampicillin, or nitrofurantoin (a urinary antiseptic antibiotic used in humans) are common choices. The basis of prophylactic antibiotic therapy is to provide $\frac{1}{3}$ to $\frac{1}{2}$ of the total daily dose of an antibiotic usually at night after the last void of the day. Antibiotics concentrate in the urinary bladder overnight preventing colonization of the urine. The daily treatments are continued for 6 months with monthly cultures to ensure a breakthrough infection has not occurred. After 6 months if the urine remains sterile the antibiotics can then be discontinued and the therapy repeated as necessary.

A final group of UTI preventatives is bacterial interference. This therapy uses the theory that colonization of the urinary bladder with nonvirulent organisms may outcompete and prevent infection with more virulent bacteria. This is also the basis for monitoring and not treating patients with asymptomatic bacteriuria (ASB) or subclinical bacterial colonization of the urinary bladder. In people the treatment of ASB is not recommended in many circumstances since ASB clearance does not prevent future infection and the presence of ASB may actually be protective. Evidence demonstrating the benefit of ASB in veterinary medicine is lacking. The decision to treat or monitor is a challenging one since subtle clinical signs and pyelonephritis can be missed, but in patients with recurrent resistant bacteriuria this option should be considered if the underlying cause of recurrent UTI cannot be addressed. Situations where cautious monitoring can be considered is with attentive owners that have pets lacking clinical signs of UTI and pyelonephritis while also lacking hematuria, pyuria, fever, a leukocytosis, and azotemia. In these patients I will have owners check their pets temperature and measure hematuria using a urine dipstick 1-2x per week. If they note a temperature increase, hematuria, or changes in clinical signs I will then institute therapy. This is by no means a foolproof method and hence must only be considered with a strong understanding of the patient's overall health and after discussing the pros and cons of not treating the bacteriuria with owners.

Other forms of bacterial interference include the intravesicular instillation of nonpathogenic *E. coli* to try and establish an ASB and the use of probiotics. Thus far nonpathogenic *E. coli* instillations lack clinical studies in veterinary medicine, although they are ongoing. As for probiotics, *Lactobacillus* and other lactic acid producing bacteria are theorized to decrease vaginal pH thereby inhibiting uropathogenic bacterial colonization. In female dogs the importance of *Lactobacillus* as a vaginal colonizer is not known as it sporadically colonizes the vaginal vault of dogs with recurrent UTI and normal spayed female dogs. Orally supplementing female dogs with lactic acid producing bacteria fails to alter the vaginal population suggesting that oral supplements containing lactic acid producing bacteria are of limited utility for preventing reinfection in dogs. Similarly, the use of estrogens also helps to prevent reinfection in women by altering the urinary microenvironment by promoting vaginal *Lactobacillus* growth, lowering vaginal pH, and restoring atrophic mucosa within the urethra. Vaginally applied and not orally administered estrogen supplements reduce the number of recurrent UTIs in postmenopausal women. It is unknown how this treatment translates to dogs and cats, however patients with subclinical USMI may benefit from estrogen therapy.