# CHANGING PARADIGMS REGARDING UTI IN MAN AND BEAST

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Maybe you have had bacterial cystitis yourself once or twice and wondered why people are treated for urinary tract infections (UTI) so differently than we treat dogs with simple cystitis. Here is a review of current recommendations and how guidelines are changing, including what to do when 'nasty' resistant organisms are found in the urine of dogs which have no clinical signs of UTI.

## DURATION OF ANTIBIOTIC TREATMENT FOR HUMANS WITH BACTERIAL UTI

Overuse and misuse of antibiotics in hospital and community settings have concerned medical workers for many years now, because of the emergence of bacterial resistance, adverse effects for patients, and possibly unjustifiable rising health care costs. In 2003, a Cochrane review showed that for acute uncomplicated cystitis in children, a 2-4 day course of oral antibiotics was just as effective in eradicating bacterial infection as a 7-14 day course.[1] In 2005, a similar Cochrane review showed 3 days of treatment was as good as 5-10 days for a symptomatic cure for uncomplicated UTI in women, although the longer course was more helpful for eradication of infection albeit with more adverse effects.[2] In 2011, short-term antibiotic treatment (even sometimes single dose) was accepted as standard of care for simple uncomplicated acute cystitis in women.[3] Recommendations for women with **uncomplicated cystitis** by the Infectious Diseases Society of America (IDSA) include the following options:

1.nitrofurantoin monohydrate/macrocrystals100 mg PO q12h x 5d, to be avoided if pyelonephritis is suspected

2.trimethoprim-sulfamethoxasole (TMS) 160/800 mg (one DS tablet) PO q12h x 3d, to be avoided if resistance prevalence exceeds 20% or if the patient has used TMS for UTI in the last 3 months

3.fosfomycin trometamol 3 g single dose PO, to be avoided if pyelonephritis is suspected

4.pivmecillinam 400 mg PO q12h x 5d (or 3-7d), to be avoided if pyelonephritis is suspected

5.fluoroquinolones PO x 3d, if none of the above can be used

6.beta-lactams such as clavulinic acid/amoxicillin (avoid amoxicillin alone) PO x 3-7d, but this is least favored.

IDSA recommendations for women with **acute pyelonephritis** include these commonly used options (with culture/sensitivity):

1.oral ciprofloxacin 500 mg PO q12h x 7d with or without an initial intravenous dose of ciprofloxacin 400 mg, unless resistance prevalence in the area exceeds 10%

2.an initial one-time intravenous dose of antibiotic may be used, especially before sensitivity results are known, such as 1 g ceftriaxone or a consolidated 24h dose of an aminoglycoside, followed by oral fluoroquinolone or TMS

3.once daily extended release oral ciprofloxacin (1000 mg) PO x 7d or levofloxacin 750 mg PO x 5d

4.oral TMS one DS tablet PO q12h x 14d

5.beta-lactam antibiotics are less effective for pyelonephritis in people

6.hospitalized patients with pyelonephritis should initially get an intravenous regimen, for example one of the following: fluoroquinolone; aminoglycoside with or without ampicillin; extended spectrum cephalosporin or extended spectrum penicillin, with or without aminoglycoside; or carbapenem.

## DURATION OF ANTIBIOTIC TREATMENT FOR DOGS WITH BACTERIAL UTI

Similarly, the International Society for Companion Animal Infectious Diseases (ISCAID) addressed the issue and questioned the need for antibiotic treatment of long duration, such as the common protocols used for UTI in small animals.[4] Historically, simple uncomplicated acute bacterial cystitis in small animal veterinary cases has been treated with 10-14 days of antibiotic therapy. Several studies challenge that old dogma.[5,6] Comparison of a short-term high dose protocol with a commonly used regimen in dogs (enrofloxacin 18-20 mg/kg PO q24h x 3d vs. amoxicillin-clavulanic acid 13.75-25 mg/kg PO q12h x 14d) showed no significant differences in clinical

(88.6% vs 87.9%) nor microbiological (77.1% vs 81.2%) cure rates.[5] Likewise, no differences were found in clinical or microbiological cure rates, even 30 days after cessation of therapy, when comparing a short- and longer-term protocol (TMS 15 mg/kg PO q12h x 3d vs. cephalexin 20 mg/kg PO q12h x 10d) in female dogs with uncomplicated bacterial cystitis.[6]

Chronic, recurrent, or otherwise complicated cystitis in dogs is generally treated longer (3-4 weeks) and pyelonephritis and prostatitis in small animals are usually treated for 4-8 weeks. In people, pyelonephritis is only treated for 5-7 days with as good responses. Studies are needed in veterinary medicine to see if duration of treatment for pyelonephritis and prostatitis may be modified to shorter duration protocols.

**RESISTANT BACTERIAL UTI AND ZOONOTIC POTENTIAL**

The vast majority of bacterial UTIs in both human and veterinary patients are due to uropathogenic *E. coli* (UPEC) infections. There is concern that overuse/abuse of antibiotics has led to bacterial resistance, especially causing multiple drug resistance (MDR) strains. Antibiotic resistance can be transmitted horizontally between bacteria, even from other bacterial species, by conjugation and transfer of plasmids which hold resistance genes, e.g., ESBL (Extended Spectrum -Lactamase) and AmpC -lactamase genes, which can be detected by PCR testing. PCR technology can also be used to detect urovirulence genes, for instance that encode type 1 fimbriae (*fimH*), pili associated with pyelonephritis (*pap*), S and F1c fimbriae (*sfa* and *foc*), afimbrial adhesins (*afa*), cytotoxic necrotizing factor (*cnf*), hemolysin (*hly*), and aerobactin (*aer*). Luckily, just because bacteria are resistant does not mean they are more pathogenic or virulent than other strains, in fact they may be less so! Wagner[7] showed that MDR strains of *E. coli* tended to be commensal, with fewer virulence genes, and so may not be as pathogenic. That study also found no evidence for zoonotic potential for either susceptible or MDR strains. In contrast, the human strain O25b:H4-ST131 *E. coli* is both MDR and highly virulent and there is potential for sharing of bacterial strains in households (although human-to-dog transmission may predominate).[8] Uropathogenic *E. coli* canine isolates can invade human bladder epithelial cells.[9]

When a urine culture shows MDR bacterial growth, consider whether or not aggressive treatment with expensive injectable antibiotics such as imipenem, meropenem, aminoglycosides, etc., is truly warranted for the individual. If there are no clinical signs of illness (and if the animal is not immunosuppressed or otherwise at risk for pyelonephritis or sepsis), perhaps treatment can be withheld and the patient monitored carefully. Over time the MDR strains may become more sensitive or they may be replaced by other less resistant bacteria in the biofilm.

If resistant strains must be treated, consider alternative antibiotics (rather than the 'big guns' mentioned above) which are not used commonly. For instance, nitrofurantoin is oral and is less likely to cause bacterial resistance (but realize it may have a higher adverse reaction rate, e.g., gastrointestinal, hepatic, neurologic signs, hypersensitivity). Fosfomycin is oral and may be useful for resistant MDR infections; in people it is given as a high single dose, since bacteria may become resistant to it quickly. Tidbits about fosfomycin include nephrotoxicity in cats, it is fairly expensive, and it should not be given within 2 hours of tetracycline drugs or metoclopramide.

**SHOULD WE TREAT NON-CLINICAL UTI IN DOGS?**

Subclinical (asymptomatic) bacteriuria is very common in women, increasing with age (seen in 5% of pre-menopausal women, 25% of women > 65 years of age, and in 50% of women over 80 years of age).[10] Treatment is not automatically recommended unless they are immunosuppressed, at risk for sepsis, or otherwise impaired. Researchers are studying the prevalence of subclinical UTI in dogs. Wan[11] found 12% of young/middle-aged dogs and 6% of senior/geriatric dogs had subclinical UTI, averaging 8.9% of dogs, which had no clinical signs over a 3-month observation period. McGhie[12] found 2.1% of dogs (actually 4.4% of female dogs) had no clinical signs of UTI although they had positive urine cultures. As stated above, Wagner[7] found that just because an isolate has an MDR pattern does not make it pathogenic. Thus we should consider in our patients whether they really need to be treated or whether judicious monitoring is warranted. Treatment may actually be contraindicated, since bacteria of low pathogenicity may be protective, by competing and inhibiting the colonization of more pathogenic strains.[8,13] A diverse group of commensal bacteria genera have been found in healthy canine urogenital tracts.[13]

**PREVENTIVE POSSIBILITIES**

When clinical UTI is recurrent or chronic, besides appropriate antibiotic therapy based on culture and sensitivity testing, and monitoring of urine tests during and after antibiotics are stopped, a diagnostic work-up to search for underlying predispositions is recommended. For instance, local disease (urinary calculi, tumors, polyps, remnant suture nidus, or abnormal storage/emptying) or systemic disease associated with infection or immunosuppression (hyperadrenocorticism, diabetes, cancer, exogenous drugs), neurologic, orthopedic, or metabolic disease need to be addressed to eliminate predisposition for relapse. In some frustrating cases, other 'tricks' are sought, and below are some ideas. In most cases blinded well-controlled studies are lacking, or evidence is weak, for recommending a group of supplements purporting to help prevent UTI. Nevertheless, when faced with an individual that is predisposed to recurrent infection, along with specific, perhaps prolonged, antimicrobial therapy, the following may be considered.

1.Cranberry products.[14-16] The 2012 Cochrane review showed a very small trend (although not significant) that cranberry products decreased UTI episodes in women compared to placebo or no treatment. Juice, tablets, and capsules are available. An active ingredient, proanthocyanidins (PAC), is found in products such as Crananidin® (Nutramax) and may be worth trying. This cranberry substance decreases *E. coli* adherence to uroepithelial cells and biofilm and may also help decrease some *Staphylococcus* and other spp colonization. The activity is dose dependent and since most products are not standardized for PAC content, it is difficult to compare and study these products. In people, the recommended dose of PAC-standardized cranberry powder is 72 mg of PAC per day.[16]

2.Methenamine hippurate (Hiprex) or methenamine urate (Urex).[17] Methenamine forms formaldehyde in an acid environment, which is then hostile to microbial growth. Urinary acidifiers such as ammonium chloride probably work better than methionine or vitamin C to acidify the urine and may be given concurrently to help keep the urinary pH low enough for methenamine to work; acid urine may also be hostile to microbial growth. The dose of methenamine is 500 mg PO q12h for dogs and 250 mg PO q12h for cats, to be taken with food. The Cochrane review showed it to be helpful in preventing UTI in people that do not have renal tract abnormalities such as neuropathic bladder.

3.When urinary catheters are used, there is a risk for biofilm to develop on the catheter and for increased risk for UTI. Using catheters coated with chlorhexidine was shown to decrease risk for UTI in dogs.[18]

4.If polyuria/polydipsia (PU/PD) is occurring, atonic bladder (from 'being good') may increase the risk for UTI because of inadequate emptying during voiding, and thus stagnation that interferes with the natural defense mechanism of emptying the bladder to flush out microbial growth in the urinary tract. Treatment of the underlying cause of PU/PD will hopefully help, but if this is not possible, consider helping the bladder to empty with careful doses of the cholinergic urecholine (Bethanechol). Bethanechol will not be able to work if the bladder is so overfull that the tight junction apparatus between detrusor muscle cells is unable to work, therefore the bladder must be maintained at least partly empty enough for bethanechol to have a chance to work (by manual expression, or if necessary, intermittent catheterization q8h). The main side effects of Bethanechol are cholinergic stimulation causing salivation, nausea, vomiting, diarrhea, lacrimation, etc. In particular cats can be quite sensitive, and only very low doses should be used as a starting dose (1.25 mg per small dog/cat).

5.Avoid drugs which favor incomplete emptying of the bladder. H1 antihistamines may cause retention of urine. Similarly, products which allow the detrusor muscle to relax and for the bladder to fill (possibly overfill) such as anticholinergics and beta-agonists, or products which increase urethral tone, e.g., phenylpropanolamine (used for urinary incontinence), may need to be withdrawn or decreased in dosage to help decrease the risk for urinary retention in the face of UTI.

6.Consider pain-relievers and NSAIDs (non-steroidal anti-inflammatory drugs) for orthopedic cases which cause inability to posture long enough to completely empty the bladder during voiding. Avoid NSAIDs in dogs with hyperadrenocorticism or those which are getting treated with exogenous steroids for immune-mediated, oncologic, or other conditions.

7.Yogurt or probiotics with lactobacillus do not appear helpful. Lactic acid-producing bacteria are not commonly found in the healthy canine vaginal vault, and an oral probiotic supplement given for 2-4 weeks did not change that flora.[19] In addition, vaginal microbiota is not different in spayed dogs with a history of recurrent UTI compared with controls.[20]

8.Low-dose long-term antibiotic therapy (one-third to one-half the daily dose given just at bedtime, with urine culture monitoring every 4-8 weeks) has been advocated by some for refractory cases,[21,22] although

evidence for prevention of recurrent UTI is lacking.[4] Evidence is lacking for instillation of intravesicular antimicrobials.[21]

9.Future directions: 1) vaccination against uropathogenic *E. coli* infections,[23] 2) the deliberate colonization of the bladder with commensal (non-pathogenic) strains of bacteria to stimulate immunity and compete with more pathogenic bacteria,[24,25] and 3) using combinations, e.g., N-acetylcysteine/D-mannose and *Morinda citrifolia* fruit extract, or cranberry/D-mannose/propolis extract, to decrease the frequency of recurrent UTI episodes.[26,27]

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